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Original Communications

FACTORS POSSIBLY INFLUENCING THE RETENTION OF CALCIUM, PHOSPHORUS, AND NITROGEN BY INFANTS GIVEN WHOLE MILK FEEDINGS

I. THE CURDING AGENT

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UNMODIFIED whole sweet milk is not readily digested by young infants, but abundant clinical observation now attests that whole milk acidified with lactic acid to the point of formation of a fine curd can be well utilized even by very young infants.[1] It is known that evaporated milk forms a fine curd in the stomach, a curd similar in many respects to that of human milk. Brennemann[2] has found that the clinical results were equally excellent when either acidified or unacidified evaporated milk was fed, and he has concluded that the fineness of the curd rather than decreased buffer capacity was responsible for the improved utilization.

A finely divided curd with its increased surface for action of digestive juices might be expected to increase the absorption and therefore the retention of nitrogen. It seems possible, however, that acidification of the milk might be an additional aid in the absorption of calcium. In order to determine the effect of the method of preparation of the feeding upon the retentions of nitrogen, calcium, and phosphorus, infants have been given boiled fresh whole milk feedings curded by means of lactic or citric acid or by the addition of a pepsin-rennin preparation, or evaporated milk untreated except for dilution to the equivalence of whole milk or slightly less for the younger infants. Each of these methods of preparation of the feeding permits the production of a fine curd in the infant's stomach, though the buffer value is altered appreciably only with the acid additions.

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The expenses of this investigation were defrayed in part by Mead Johnson and Company, Evansville, Indiana.

The feedings of each type contained 6 per cent of added carbohydrate, consisting of a dextrin-maltose mixture. Each infant received one teaspoonful of cod liver oil daily, containing approximately 350 U.S.P. units of vitamin D. The customary additions to the diet were given each infant at the same age, viz., 1 ounce of orange juice was given daily to infants under four months of age, 2 ounces to older infants; an egg yolk was added to the feeding at four months, sieved vegetables were given at five months, and sieved fruits at six months.

The acid milks contained 4 to 4.5 c.c. of 85 per cent lactic acid or 10 c.c. of 25 per cent citric acid per liter. The pepsin-rennin prepara-

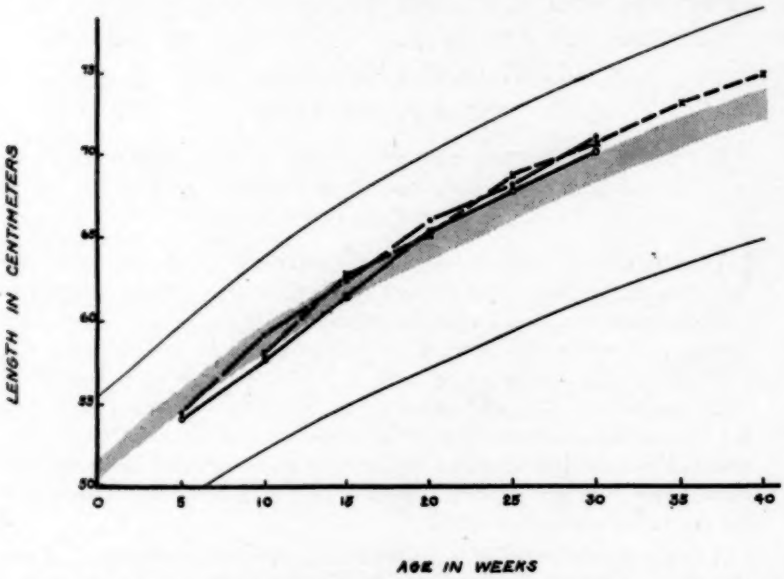

Chart 1.—Average growth in length of infants given feedings of whole milk with 6 per cent carbohydrate addition.
o———o Infants given milk acidified with organic acid.
.— — —. Infants given milk curded with pepsin-rennin solution.
x- - - - -x Infants given unacidified evaporated milk.
The shaded portion represents the average range, and the fine lines the limit of normal of the Kornfeld growth standards[7].

tion used contained 2 c.c. of 85 per cent lactic acid per liter; 10 c.c. of the solution was added to a liter of milk, making the final added acid concentration less than 0.002 per cent. The effectiveness of this preparation may thus be ascribed wholly to the enzyme action. The evaporated milk was diluted with an equal volume of 12 per cent carbohydrate solution for the older infants, and with two volumes of 9 per cent carbohydrate solution for the very young infant. In order to preclude, if possible, the necessity for use of protein for energy, the daily caloric intake of the infants was kept as high as practicable.

The average ingestion varied from approximately 140 calories per kilogram for the younger infants to 120 calories per kilogram for the older ones.

Four infants for varying lengths of time were given boiled fresh milk acidified with lactic acid, then citric acid was substituted for lactic acid; five other infants were given the citric acid milk exclusively. One infant received evaporated milk acidified with lactic acid. Eight infants were fed rennin milk mixtures, and four the unacidified evaporated milk feedings. Three of this latter group had previously been given acidified evaporated milk, and a summary of the findings has been reported.[3]

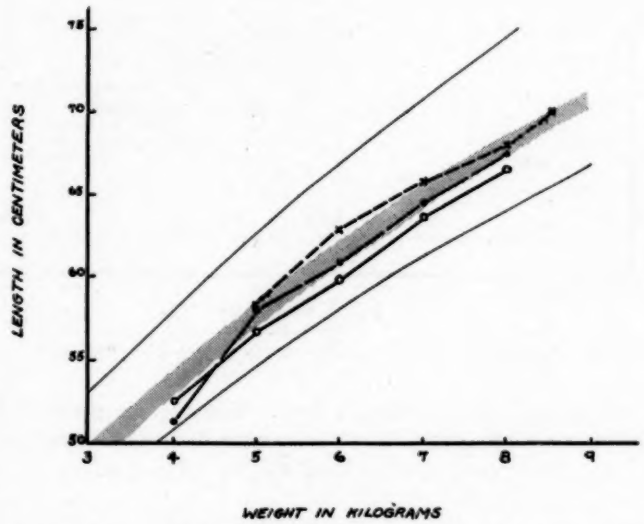

Chart 2.—Average growth in weight for length of infants given feedings of whole milk with 6 per cent carbohydrate addition.
o———o Infants given milk acidified with organic acid.
.— — —. Infants given milk curded with pepsin-rennin solution.
x- - - - -x Infants given unacidified evaporated milk.
The shaded portion represents the average range, and the fine lines the limit of normal of the Kornfeld growth standards[7].

The general ward and laboratory procedures have been discussed in detail elsewhere.[3] Accurate records were kept of growth, both in length and weight, and of muscular achievement at various ages; roentgenograms of wrist and ankle were obtained at four-week intervals. The metabolism periods were of three days' duration. The analyses of food and excreta were made according to standard procedures; calcium was determined by a modification of the McCrudden technic,[4] phosphorus by the method of Fiske and Subbarow,[5] and nitrogen by the Kjeldahl-Gunning procedure.[6]

RESULTS

Clinically, all of the milk feedings used seemed equally effective. The stools of those infants fed the unacidified milks tended to be more formed in character than did those of the infants fed the acid milks. All of the infants grew both in length and weight, at somewhat greater rates than the average standards.[7] No differences in rate of growth

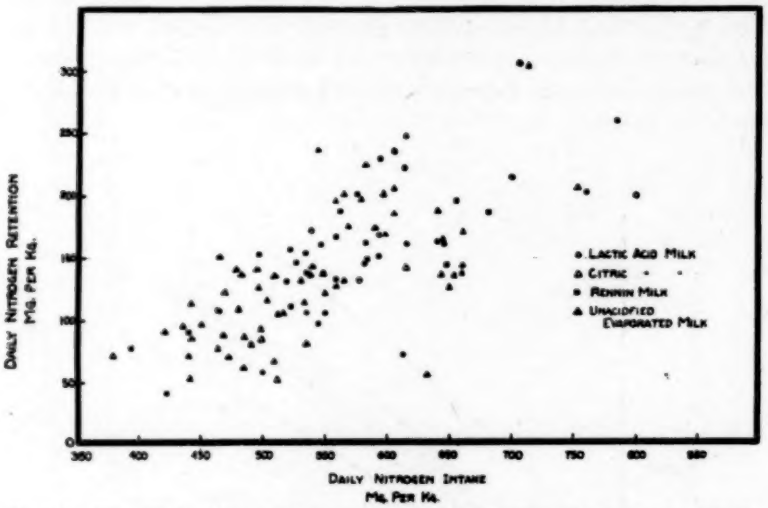

Chart 3.—The effect of the curding agent upon the retention of nitrogen by infants given whole milk feedings.

could be ascribed to the different diets. The average growth curves are shown in Charts 1 and 2. Bone growth and calcification, as evidenced by roentgenographic examinations, were normal for each infant.

TABLE I

URINARY EXCRETION OF CITRIC ACID BY INFANTS

NAME	ACID ADDED TO MILK	AGE WK.	CITRIC ACID INGESTED GM. PER DAY	AVERAGE URINARY EXCRETION CITRIC ACID GM. PER DAY
R—n	Lactic	18	1.57	0.191
		20	1.47	0.176
	Citric	28	3.85	0.189
C—r	Lactic	11	2.72	0.132
		13	1.98	0.138
	Citric	15	3.72	0.194
		18	5.02	0.150
G—e	Lactic	8	1.62	0.206
		10	1.71	0.184
	Citric	16	4.62	0.213
K—n	Lactic	7	1.56	0.088
	Citric	10	3.16	0.097

In order to determine the utilization of citric acid by infants, the citric acid excretion in the urine of four infants was studied when the infants were given lactic acid milk, and when the citric acid milk was

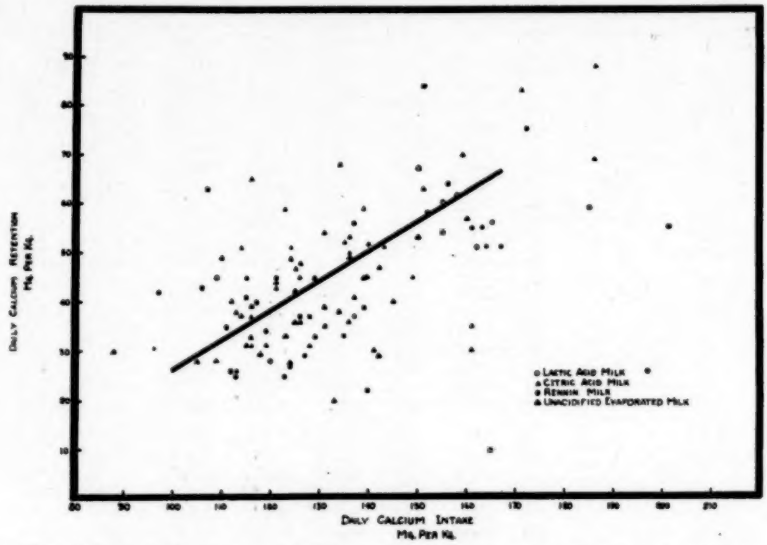

Chart 4.—The effect of the curding agent upon the retention of calcium by infants given whole milk feedings.

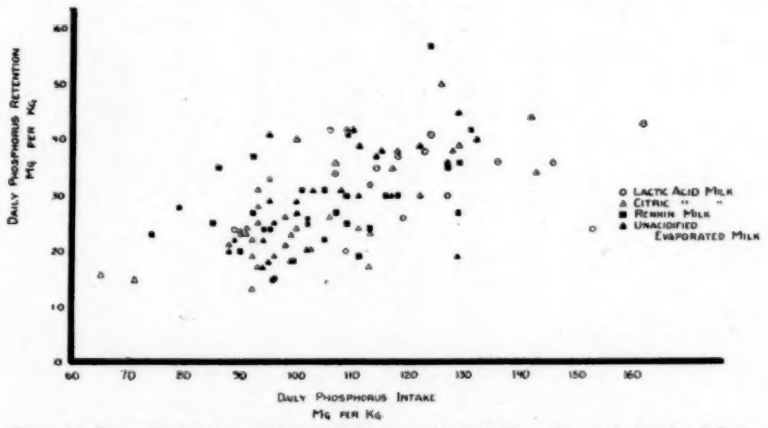

Chart 5.—The effect of the curding agent upon the retention of phosphorus by infants given whole milk feedings.

fed. We are indebted to Dr. Adrian Kuyper, of the department of biochemistry, for these analyses. The results, given in Table I, demonstrate that the added citric acid was almost completely oxidized, causing no added burden to the kidneys.

TABLE

DAILY RETENTION OF CALCIUM, PHOSPHORUS AND NITROGEN BY INFANTS

NAME DATE OF BIRTH	CURD MODIFIER	AGE WK.	WEIGHT GM.	LENGTH CM.	CA INTAKE TOTAL GM.	CALCIUM EXCRETION URINE GM.	CALCIUM EXCRETION FECES GM.	CALCIUM EXCRETION TOTAL GM.	CALCIUM RETENTION TOTAL GM.	CALCIUM RETENTION PER KG. GM.
R—n	L. A.*	12	5397	----	1.089	0.025	0.762	0.787	0.302	0.056
11/10/30		14	6130	60.0	1.132	0.018	0.755	0.773	0.359	0.059
		16	6552	61.0	0.937	0.023	0.525	0.548	0.389	0.060
		18	6925	62.4	1.046	0.047	0.567	0.614	0.432	0.063
		20	7455	63.8	0.810	0.034	0.444	0.478	0.332	0.045
	C. A.†	22	7512	65.7	0.884	0.024	0.524	0.548	0.336	0.045
		24	7712	67.0	0.848	0.019	0.426	0.445	0.402	0.049
		28	8300	68.4	1.207	0.036	0.735	0.771	0.436	0.052
		31	8300	69.6	1.130	0.021	0.697	0.718	0.412	0.050
		34	8600	72.2	1.075	0.040	0.596	0.636	0.439	0.051
C—r	L. A.	9	5235	58.0	1.149	0.007	0.966	0.973	0.176	0.034
1/5/31		11	5412	58.5	0.874	0.005	0.590	0.595	0.279	0.051
		13	5743	59.0	0.875	0.003	0.541	0.544	0.331	0.058
	C. A.	15	6050	60.2	0.964	0.003	0.536	0.539	0.425	0.070
		18	6250	62.0	0.896	0.013	0.491	0.504	0.392	0.051
		23	6755	64.8	0.958	0.038	0.716	0.754	0.204	0.030
		26	7025	66.0	0.956	0.038	0.546	0.584	0.372	0.053
G—e	L. A.	8	5150	56.0	0.796	0.011	0.506	0.517	0.279	0.054
1/17/31		10	6025	56.8	0.988	0.017	0.641	0.658	0.330	0.056
		12	6690	58.0	0.999	0.027	0.528	0.555	0.444	0.067
	C. A.	16	7675	60.6	1.001	0.043	0.694	0.737	0.264	0.035
		18	8190	62.6	0.928	0.044	0.571	0.615	0.313	0.038
		20	8400	65.0	0.916	0.017	0.651	0.658	0.238	0.028
		22	8600	66.3	0.994	0.039	0.506	0.545	0.449	0.052
		24	8730	67.5	0.764	0.040	0.464	0.504	0.260	0.030
K—n	L. A.	7	4500	56.5	0.886	0.017	0.750	0.767	0.119	0.026
2/17/31	C. A.	10	5435	57.5	1.017	0.016	0.626	0.642	0.375	0.069
	C. A.	14	6360	59.7	0.957	0.011	0.662	0.673	0.284	0.044
R—s	C. A.	12	5670	60.0	0.790	0.020	0.434	0.454	0.336	0.059
3/26/32		14	5875	61.0	0.729	0.017	0.423	0.440	0.289	0.049
		15	6000	61.2	0.771	0.013	0.572	0.585	0.186	0.031
		16	6150	61.8	0.715	0.017	0.508	0.525	0.190	0.031
P—n	C. A.	7	4825	55.0	0.897	0.014	0.466	0.480	0.417	0.088
3/17/33		10	5600	56.3	0.960	0.024	0.471	0.495	0.465	0.083
		13	6475	58.3	0.799	0.050	0.370	0.420	0.379	0.059
		17	7000	61.2	0.845	0.073	0.469	0.542	0.303	0.043
		18	7200	62.7	0.900	0.060	0.499	0.559	0.341	0.047
A—g	C. A.	20	7350	67.8	1.000	0.023	0.715	0.738	0.262	0.036
3/19/32		22	7800	68.2	1.019	0.037	0.674	0.711	0.308	0.039
		23	8110	68.5	0.944	0.043	0.604	0.647	0.297	0.037
B—n	C. A.	13	7125	64.8	1.142	0.032	0.896	0.928	0.214	0.030
3/4/32		15	7850	65.5	1.016	0.018	0.745	0.763	0.257	0.033
		17	8200	66.5	1.121	0.011	0.773	0.784	0.337	0.041
		19	8430	68.5	1.117	0.017	0.928	0.945	0.172	0.020
		27	9460	71.3	1.125	0.035	0.787	0.822	0.303	0.031
		29	9825	71.6	1.140	0.054	0.760	0.813	0.327	0.033
H—r	C. A.	14	6300	60.0	1.019	0.018	0.780	0.798	0.221	0.035
4/11/32		16	6625	61.0	0.960	0.016	0.676	0.692	0.268	0.040
		22	8000	66.2	0.900	0.016	0.566	0.582	0.318	0.040
S—s	L. A.	16	6137	62.6	0.933	0.014	0.546	0.560	0.373	0.061
7/1/31	Evap. milk	18	6413	64.0	0.769	0.013	0.578	0.591	0.178	0.028
		20	6600	65.0	0.906	0.017	0.644	0.661	0.244	0.037

*Lactic acid.
†Citric acid.

II

GIVEN MILK MIXTURES ACIDIFIED WITH LACTIC AND CITRIC ACID

P INTAKE	PHOSPHORUS EXCRETION			PHOSPHORUS RETENTION		N INTAKE	NITROGEN EXCRETION			NITROGEN RETENTION	
TOTAL GM.	URINE GM.	FECES GM.	TOTAL GM.	TOTAL GM.	PER KG. GM.	TOTAL GM.	URINE GM.	FECES GM.	TOTAL GM.	TOTAL GM.	PER KG. GM.
0.790	0.528	0.069	0.597	0.193	0.036	3.78	1.86	0.76	2.62	1.16	0.215
0.830	0.408	0.142	0.550	0.280	0.046	4.35	1.97	0.50	2.47	1.88	0.306
0.700	0.398	0.079	0.477	0.223	0.034	3.48	2.77	0.23	3.00	0.48	0.073
0.787	0.420	0.076	0.496	0.291	0.042	4.28	2.46	0.27	2.73	1.55	0.224
0.664	0.397	0.086	0.483	0.181	0.024	3.46	2.45	0.21	2.66	0.80	0.107
0.739	0.428	0.116	0.544	0.195	0.026	3.78	2.98	0.41	3.39	0.49	0.066
0.707	0.406	0.076	0.482	0.225	0.029	3.48	2.50	0.23	2.73	0.75	0.097
1.061	0.561	0.182	0.743	0.318	0.038	4.24	3.51	0.31	3.82	0.42	0.051
0.979	0.533	0.134	0.667	0.311	0.038	5.01	3.03	0.30	3.33	1.67	0.202
0.935	0.430	0.137	0.567	0.368	0.042	4.80	2.82	0.29	3.11	1.69	0.197
0.851	0.406	0.220	0.626	0.225	0.043	4.30	1.72	0.27	1.99	2.31	0.440
0.646	0.399	0.107	0.506	0.140	0.026	3.20	2.07	0.22	2.29	0.91	0.168
0.652	0.314	0.109	0.423	0.229	0.042	3.08	1.77	0.32	2.09	0.99	0.172
0.771	0.386	0.081	0.467	0.304	0.050	4.30	2.26	0.20	2.46	1.84	0.304
0.735	0.416	0.053	0.469	0.266	0.035	3.85	2.75	0.20	2.95	0.90	0.144
0.825	0.477	0.142	0.619	0.206	0.030	4.46	3.10	0.21	3.31	1.15	0.170
0.770	0.359	0.153	0.512	0.258	0.036	4.05	2.37	0.28	2.65	1.40	0.198
0.632	0.326	0.109	0.435	0.197	0.038	3.12	1.71	0.19	1.90	1.22	0.236
0.766	0.514	0.070	0.584	0.182	0.030	3.69	2.46	0.26	2.72	0.97	0.161
0.765	0.443	0.084	0.527	0.238	0.036	3.85	2.65	0.31	2.96	0.89	0.133
0.784	0.554	0.080	0.634	0.150	0.020	3.16	2.95	0.21	4.04	0.88	0.115
0.816	0.552	0.115	0.667	0.149	0.018	4.20	3.10	0.23	3.33	0.87	0.106
0.772	0.509	0.156	0.665	0.107	0.013	4.17	2.86	0.24	3.10	1.07	0.127
0.781	0.474	0.106	0.580	0.201	0.023	3.81	2.82	0.26	3.08	0.73	0.085
0.615	0.399	0.084	0.483	0.132	0.015	3.30	2.42	0.26	2.68	0.62	0.071
0.687	0.436	0.142	0.578	0.109	0.024	3.61	2.16	0.55	2.71	0.90	0.200
0.777	0.559	0.037	0.596	0.181	0.034	4.08	2.68	0.28	2.96	1.12	0.206
0.728	0.587	0.035	0.622	0.106	0.017	3.81	2.28	0.27	2.55	1.26	0.200
0.566	0.311	0.031	0.342	0.224	0.040	3.20	1.89	0.17	2.06	1.14	0.201
0.559	0.325	0.038	0.363	0.196	0.033	2.72	1.88	0.39	2.27	0.45	0.077
0.554	0.343	0.057	0.400	0.154	0.026	2.91	1.96	0.43	2.39	0.52	0.087
0.537	0.365	0.044	0.409	0.128	0.021	2.89	1.79	0.34	2.13	0.76	0.123
0.674	0.447	0.018	0.465	0.209	0.044	2.30	1.57	0.28	1.85	0.45	0.093
0.722	0.489	0.014	0.503	0.219	0.039	3.51	2.72	0.48	3.20	0.31	0.055
0.601	0.394	0.025	0.419	0.182	0.028	2.84	2.12	0.37	2.49	0.35	0.054
0.628	0.428	0.021	0.469	0.159	0.023	3.52	2.46	0.27	2.73	0.79	0.113
0.671	0.424	0.026	0.450	0.221	0.031	3.80	2.47	0.38	3.80	0.95	0.132
0.830	0.560	0.100	0.660	0.170	0.023	4.85	2.95	0.48	3.43	1.02	0.139
0.780	0.455	0.140	0.595	0.185	0.024	4.66	2.50	0.46	2.96	1.70	0.218
0.733	0.417	0.127	0.544	0.189	0.023	4.27	2.37	0.79	3.16	1.11	0.137
0.793	0.575	0.047	0.622	0.171	0.024	4.65	3.22	0.46	3.68	0.97	0.136
0.769	0.549	0.057	0.606	0.163	0.021	4.30	2.91	0.43	3.34	0.96	0.123
0.816	0.516	0.115	0.631	0.185	0.023	4.07	2.78	0.59	3.37	0.70	0.085
0.773	0.472	0.096	0.588	0.205	0.024	4.13	2.82	0.62	3.44	0.69	0.082
0.907	0.639	0.092	0.731	0.176	0.019	4.17	2.59	0.48	3.07	1.10	0.115
0.915	0.633	0.114	0.747	0.168	0.017	4.28	2.83	0.52	3.35	0.93	0.095
0.711	0.521	0.081	0.602	0.109	0.017	4.05	2.65	0.53	3.18	0.87	0.138
0.705	0.479	0.054	0.533	0.172	0.026	4.28	2.72	0.47	3.19	1.09	0.165
0.734	0.475	0.082	0.557	0.177	0.022	4.10	2.68	0.56	3.24	0.86	0.105
0.759	0.390	0.115	0.505	0.254	0.041	3.78	1.73	0.53	2.26	1.52	0.248
0.702	0.423	0.154	0.574	0.128	0.020	3.21	2.35	0.49	2.84	0.37	0.058
0.781	0.482	0.119	0.601	0.180	0.037	3.85	2.55	0.55	3.10	0.70	0.106

TABLE

DAILY RETENTION OF CALCIUM, PHOSPHORUS AND NITROGEN BY INFANTS

NAME DATE OF BIRTH	CURD MODIFIER	AGE WK.	WEIGHT GM.	LENGTH CM.	CA IN-TAKE TOTAL GM.	CALCIUM EXCRETION URINE GM.	CALCIUM EXCRETION FECES GM.	CALCIUM EXCRETION TOTAL GM.	CALCIUM RETENTION TOTAL GM.	CALCIUM RETENTION PER KG. GM.
L—e	R*	10	5840	57.0	0.912	0.018	0.519	0.537	0.375	0.064
3/25/31		12	6340	58.8	0.886	0.025	0.613	0.638	0.248	0.039
		14	6835	61.0	0.933	0.026	0.526	0.552	0.381	0.059
		17	7525	63.0	0.932	0.026	0.703	0.729	0.203	0.027
		19	8000	64.2	1.031	0.031	0.634	0.668	0.363	0.045
S—r	R	9	4790	56.6	0.724	0.013	0.308	0.321	0.403	0.084
4/10/31		11	5530	58.2	0.534	0.015	0.284	0.299	0.235	0.042
		16	5860	61.3	0.666	0.018	0.386	0.404	0.262	0.045
McC—y	R	13	5360	60.2	0.939	0.010	0.524	0.534	0.405	0.075
4/25/31		15	5480	61.6	0.893	0.010	0.580	0.590	0.303	0.055
		24	7220	66.2	0.929	0.026	0.633	0.659	0.270	0.037
		26	7433	68.0	0.952	0.032	0.641	0.673	0.279	0.037
		28	7655	69.1	0.898	0.018	0.576	0.594	0.304	0.040
		30	7900	69.8	0.971	0.018	0.758	0.778	0.195	0.025
		32	8075	70.6	0.964	0.013	0.673	0.686	0.278	0.034
		35	8400	72.9	1.032	0.026	0.656	0.682	0.351	0.042
S—z	R	15	6798	64.2	0.823	0.023	0.489	0.512	0.311	0.045
6/30/31		17	6943	65.4	0.736	0.019	0.415	0.434	0.302	0.042
		20	7020	67.0	0.791	0.014	0.594	0.608	0.183	0.026
		22	7400	68.2	0.931	0.013	0.736	0.749	0.180	0.025
		24	7825	69.6	0.876	0.013	0.661	0.674	0.202	0.026
N—n	L. A.†	18	5725	63.6	1.581	0.027	1.263	1.290	0.290	0.051
8/29/31	R	21	7000	66.5	1.138	0.022	0.757	0.799	0.359	0.051
		30	8568	73.2	1.081	0.037	0.696	0.733	0.348	0.041
G—t	R	14	5510	57.0	0.921	0.007	0.635	0.643	0.279	0.051
4/14/32										
D—r	R	19	7300	63.8	0.844	0.023	0.355	0.378	0.466	0.063
2/5/32		21	7750	64.2	0.882	0.025	0.544	0.569	0.313	0.041
		23	8100	65.2	0.902	0.031	0.588	0.619	0.283	0.035
P—n	R	15	7140	63.0	1.152	0.019	0.896	0.915	0.237	0.033
3/1/32		17	7750	63.5	1.000	0.017	0.816	0.833	0.167	0.022
		19	8000	64.2	1.121	0.019	0.871	0.890	0.231	0.029
		20	8025	64.5	1.082	0.013	0.618	0.631	0.451	0.056

*Rennin.
†Lactic acid.

The chemical data of the calcium, phosphorus, and nitrogen balance studies are given in detail in Tables II, III, and IV, for the infants given acid milks, rennin milk, and evaporated milk, respectively. Because the different infants ingested different amounts of milk, and the retentions of nitrogen and minerals depend in large measure upon the intake of these substances, the data obtained have been charted so as to determine the daily retention per kilogram of body weight for a given per kilogram intake. Different symbols have been employed to indicate the type of feeding used in each study. In general, the younger infants ingested the larger amounts of nitrogen and minerals per kilogram of body weight, although there were exceptions to this rule.

III

GIVEN MILK MIXTURES CURDLED WITH PEPSIN-RENNIN FERMENT

P IN-TAKE	PHOSPHORUS EXCRETION			PHOSPHORUS RETENTION		N IN-TAKE	NITROGEN EXCRETION			NITROGEN RETENTION	
TOTAL	URINE	FECES	TOTAL	TOTAL	PER KG.	TOTAL	URINE	FECES	TOTAL	TOTAL	PER KG.
GM.	GM.	GM.	GM.	GM.	GM.	GM.	GM.	GM.	GM.	GM.	GM.
0.689	0.376	0.134	0.510	0.179	0.030	3.76	2.50	0.34	2.84	0.92	0.160
0.645	0.329	0.155	0.484	0.161	0.025	3.51	2.18	0.27	2.45	1.06	0.167
0.750	0.364	0.103	0.467	0.283	0.041	3.94	2.19	0.37	2.56	1.38	0.200
0.790	0.402	0.224	0.626	0.164	0.023	4.37	3.85	0.41	3.26	1.11	0.148
0.772	0.418	0.160	0.578	0.194	0.024	4.40	3.23	0.33	3.56	0.84	0.105
0.595	0.269	0.053	0.322	0.273	0.057	3.06	2.09	0.20	2.29	0.77	0.161
0.409	0.232	0.050	0.282	0.127	0.023	2.18	1.57	0.18	1.75	0.43	0.078
0.461	0.243	0.063	0.306	0.165	0.028	2.58	1.79	0.26	2.05	0.53	0.090
0.703	0.371	0.107	0.478	0.225	0.042	3.64	2.32	0.31	2.63	1.01	0.188
0.654	0.361	0.094	0.455	0.199	0.036	3.68	2.33	0.28	2.61	1.07	0.196
0.791	0.437	0.176	0.612	0.178	0.025	4.20	2.81	0.24	3.05	1.15	0.160
0.864	0.455	0.183	0.638	0.226	0.030	4.38	2.93	0.33	3.26	1.12	0.151
0.804	0.388	0.178	0.566	0.238	0.031	4.58	2.48	0.36	2.84	1.74	0.230
0.846	0.429	0.203	0.632	0.214	0.027	4.42	2.57	0.33	2.90	1.52	0.190
0.821	0.429	0.183	0.607	0.214	0.020	4.41	2.77	0.35	3.12	1.29	0.160
0.874	0.455	0.185	0.620	0.254	0.030	4.43	2.81	0.36	3.17	1.26	0.150
0.623	0.320	0.133	0.453	0.183	0.027	3.59	2.42	0.22	2.64	0.95	0.139
0.585	0.283	0.128	0.411	0.174	0.025	2.83	2.28	0.26	2.54	0.29	0.042
0.711	0.359	0.136	0.495	0.216	0.030	3.67	2.64	0.25	2.89	0.78	0.111
0.822	0.447	0.237	0.684	0.138	0.019	4.12	2.85	0.28	3.13	0.99	0.133
0.774	0.430	0.201	0.631	0.143	0.018	4.04	2.69	0.32	3.01	1.03	0.132
1.238	0.648	0.374	1.022	0.216	0.038	6.27	4.28	0.48	4.76	1.51	0.260
0.901	0.513	0.203	0.716	0.185	0.027	5.48	3.34	0.31	3.65	1.81	0.260
0.941	0.524	0.163	0.687	0.254	0.030	4.64	3.14	0.38	3.52	1.12	0.130
0.702	0.415	0.094	0.509	0.193	0.035	4.19	2.63	0.43	3.06	1.13	0.204
0.629	0.315	0.059	0.374	0.255	0.035	2.62	2.28	0.24	2.52	1.10	0.151
0.734	0.434	0.115	0.549	0.185	0.024	4.07	2.56	0.58	3.14	1.13	0.146
0.727	0.427	0.135	0.562	0.165	0.020	4.72	2.45	0.49	2.94	1.18	0.146
0.806	0.517	0.115	0.632	0.174	0.024	4.63	3.18	0.42	3.60	1.03	0.145
0.741	0.525	0.097	0.622	0.119	0.015	4.23	3.05	0.42	3.47	0.76	0.098
0.769	0.493	0.155	0.648	0.121	0.015	4.27	2.75	0.29	3.04	1.23	0.154
0.740	0.341	0.103	0.444	0.296	0.037	4.17	2.34	0.48	2.82	1.25	0.156

NITROGEN

In Chart 3, the retentions of nitrogen per kilogram per day have been plotted against the daily per kilogram intakes of this element, using a different symbol to represent the retention from each type of feeding given. Each symbol represents one period of study of one infant. It is evident from the chart that the quantity of nitrogen retained tends to increase steadily with increasing intake of this element. It seems evident, also, that the range of retention for any given intake of nitrogen is practically identical for all of the milk modifications studied. No one method of preparation proved definitely superior to any other as regards nitrogen retention. It thus appears that when

TABLE IV

DAILY RETENTION OF CALCIUM, PHOSPHORUS AND NITROGEN BY IN

NAME DATE OF BIRTH	AGE WK.	WEIGHT GM.	LENGTH CM.	CA IN-TAKE TOTAL GM.	CALCIUM EXCRETION URINE GM.	CALCIUM EXCRETION FECES GM.	CALCIUM EXCRETION TOTAL GM.	CALCIUM RETENTION TOTAL GM.	CALCIUM RETENTION PER KG. GM.	P IN-TAKE TOTAL GM.
H—l	10	5130	58.0	0.641	0.002	0.456	0.458	0.183	0.036	0.492
8/16/30	12	5470	60.0	0.644	0.004	0.480	0.484	0.160	0.029	0.485
	14	6055	62.0	0.999	0.004	0.935	0.939	0.060	0.010	0.784
	19	6705	65.2	0.911	0.010	0.571	0.581	0.330	0.049	0.787
	21	6775	65.5	1.011	0.001	0.703	0.704	0.307	0.045	0.871
	23	7365	66.3	1.179	0.008	0.753	0.761	0.418	0.057	0.971
	25	7985	68.0	1.195	0.009	0.763	0.772	0.423	0.053	0.972
	27	8125	68.6	1.135	0.007	0.712	0.719	0.416	0.052	0.930
	29	7987	69.0	1.130	0.007	0.749	0.756	0.374	0.047	0.883
L—z	27	9250	70.8	1.139	0.026	0.807	0.833	0.306	0.033	0.945
5/2/30	29	9790	71.5	1.310	0.036	0.906	0.942	0.368	0.038	1.085
	34	10113	74.6	1.160	0.017	0.827	0.844	0.316	0.031	0.985
	38	10410	76.0	1.205	0.007	0.794	0.801	0.404	0.039	0.976
	40	11015	76.3	1.379	0.034	0.884	0.918	0.461	0.042	1.112
	43	11200	77.2	1.354	0.032	0.830	0.862	0.492	0.044	1.111
	45	11400	78.0	1.297	0.027	0.844	0.871	0.426	0.037	1.075
H—n	25	8705	68.8	1.089	0.050	0.723	0.773	0.316	0.036	0.937
5/20/30	37	9295	73.5	0.980	0.032	0.684	0.716	0.264	0.028	0.814
	39	9675	74.5	1.269	0.055	0.693	0.748	0.521	0.054	1.004
	41	9613	75.2	1.342	0.048	0.865	0.913	0.429	0.045	1.054
	43	9237	75.7	1.068	0.052	0.414	0.466	0.602	0.065	0.882
M—e	26	8050	68.2	1.202	0.014	0.680	0.694	0.508	0.063	1.025
5/26/30	39	8545	74.4	1.360	0.030	1.055	1.085	0.275	0.029	1.096
	42	9775	75.4	1.208	0.025	0.807	0.932	0.276	0.028	0.931

the total caloric intake is high and the milk feeding is so treated as to permit the formation of a fine curd in the infant's stomach, the quantity of nitrogen retained by an infant will vary directly with the quantity of intake of this element.

CALCIUM

Chart 4 compares the per kilogram intakes and retentions of calcium for the four groups of infants. The heavy line represents the average retention of calcium as determined from approximately 300 separate studies of infants given acidified whole milk feedings and 350 U.S.P. units of D as cod liver oil daily. It will be observed that the general trend of retention in the present study is similar to that of the larger control group, and the symbols representing retentions during the individual periods of study are about equally distributed on both sides of the average line. The range of calcium retention for any given intake is approximately the same for all of the different types of feedings. It appears, then, that organic acid added to evaporated or finely curded whole milk feedings does not result in any noteworthy increase in the amount of calcium retained by the infant.

IV

BY INFANTS GIVEN UNACIDIFIED EVAPORATED MILK MIXTURES

P IN-TAKE	PHOSPHORUS EXCRETION			PHOSPHORUS RETENTION		N IN-TAKE	NITROGEN EXCRETION			NITROGEN RETENTION	
TOTAL GM.	URINE GM.	FECES GM.	TOTAL GM.	TOTAL GM.	PER KG. GM.	TOTAL GM.	URINE GM.	FECES GM.	TOTAL GM.	TOTAL GM.	PER KG. GM.
0.492	0.248	0.116	0.364	0.128	0.025	2.47	1.38	0.38	1.76	0.71	0.138
0.485	0.254	0.109	0.363	0.122	0.022	2.72	1.62	0.33	1.95	0.77	0.141
0.784	0.391	0.278	0.669	0.115	0.019	3.99	2.46	0.66	3.12	0.87	0.143
0.787	0.389	0.195	0.584	0.203	0.030	3.80	2.28	0.63	2.91	0.89	0.132
0.871	0.280	0.288	0.568	0.303	0.045	3.99	2.08	0.73	2.81	1.18	0.174
0.971	0.450	0.224	0.674	0.297	0.040	4.72	2.83	0.51	3.34	1.38	0.188
0.972	0.439	0.221	0.660	0.312	0.039	4.82	2.80	0.55	3.35	1.47	0.185
0.930	0.420	0.205	0.633	0.297	0.037	4.72	2.42	0.49	2.89	1.83	0.225
0.883	0.394	0.181	0.575	0.308	0.039	4.29	2.66	0.48	3.14	1.15	0.144
0.945	0.473	0.281	0.754	0.191	0.020	4.99	3.51	0.74	4.25	0.74	0.081
1.085	0.485	0.311	0.776	0.289	0.030	5.45	3.34	0.85	4.19	1.26	0.129
0.985	0.506	0.293	0.799	0.186	0.018	4.75	3.56	0.48	4.04	0.71	0.070
0.976	0.525	0.290	0.815	0.174	0.017	5.02	3.39	0.49	3.88	1.14	0.110
1.112	0.509	0.283	0.792	0.320	0.029	5.34	3.65	0.62	4.67	0.67	0.061
1.111	0.545	0.269	0.814	0.297	0.027	5.23	3.72	0.58	4.30	0.93	0.088
1.075	0.554	0.276	0.830	0.245	0.022	5.03	3.88	0.57	4.45	0.58	0.051
0.937	0.412	0.254	0.666	0.271	0.031	4.77	2.99	0.57	3.56	1.21	0.139
0.814	0.414	0.208	0.622	0.192	0.020	4.31	2.81	0.51	3.32	0.99	0.107
1.004	0.522	0.179	0.701	0.303	0.031	4.90	3.17	0.42	3.59	1.31	0.136
1.054	0.414	0.236	0.650	0.404	0.042	5.20	2.30	0.60	2.90	2.32	0.238
0.882	0.375	0.129	0.504	0.378	0.041	4.28	2.62	0.28	2.90	1.38	0.150
1.025	0.466	0.269	0.735	0.290	0.036	5.23	3.54	0.68	4.22	1.01	0.126
1.096	0.331	0.385	0.716	0.380	0.038	5.33	2.90	0.76	3.66	1.67	0.175
0.931	0.374	0.279	0.653	0.284	0.029	4.66	2.72	0.56	3.28	1.38	0.141

PHOSPHORUS

As phosphorus is used both for bone and for soft tissue formation, the quantity of phosphorus retained by an infant will depend very largely upon the calcium and nitrogen retentions. The retentions of both of these elements were apparently unaffected by the various methods of preparation of feedings used. It was therefore to be expected that the phosphorus retentions likewise would be unaffected. Chart 5 shows that the daily per kilogram retention of phosphorus is increased with increasing intakes of this element, but that the range of retention for any given intake is the same whether the milk used was evaporated or curded with rennin or with acid.

SUMMARY AND CONCLUSIONS

This paper reports 108 balance studies in which were determined the retentions of nitrogen, calcium, and phosphorus by infants fed curded whole milk or evaporated milk mixtures, with 6 per cent carbohydrate additions. The quantity of vitamin D administered daily was constant throughout the experiment. In most instances the studies were continued over a sufficient period to determine the effect of the feeding

upon the growth and development of the infant. Ten infants were given whole or evaporated milk feedings acidified with lactic or citric acid; for eight infants the milk was curded by the addition of a pepsin-rennin preparation; and four infants were fed unacidified evaporated milk mixtures. All of the above milk mixtures have in common the property of permitting a fine curd in the infant's stomach.

1. The growth of each infant, both in length and weight, was somewhat above the average rate.

2. Roentgenograms of the wrist and ankle, taken at regular intervals, showed normal development and calcification of bone.

3. The retentions of the three elements studied, nitrogen, calcium, and phosphorus, all increased steadily with increasing intake. The amount of variation in retention at each intake level was approximately the same for each of the milk mixtures studied.

It is therefore concluded that if curded whole milk, or uncurded evaporated milk mixtures are fed to infants, the amounts of nitrogen and minerals available for absorption and retention are the same for any given intake of milk, whether the milk is curded by the addition of acid, by enzymes, or is altered by the long heat treatment of evaporation so that the curd formed in the stomach is small. The excellent growth and bone development, as well as the high retentions of the elements studied, constitute evidence that all of these milk mixtures are good foods for infants.

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THE RETENTIONS OF NITROGEN, CALCIUM, AND PHOSPHORUS OF INFANTS FED SWEETENED CONDENSED MILK

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THE minimal protein requirement of infants has never been actually determined. It has been generally assumed, however, that infants fed cow's milk require a considerably greater intake of protein than do breast-fed infants. A nursing infant receives about 8 per cent of his total calories in protein, whereas an artificially fed infant is said to require at least 12 per cent of his calories in protein.[1] This difference in protein requirement is explained by the higher lactalbumin content of human milk since Osborne and Mendel[2] demonstrated that less lactalbumin than casein was necessary to maintain normal growth in the rat. Edelstein and Langstein[3] attempted to prove that these findings were valid also for the human infant, but owing to the inherent difficulties of the method employed, their results were not entirely conclusive. No other similar experiments have been reported.

Although experimental evidence is lacking, most writers on infant nutrition attribute the nutritional disturbances occasionally seen in infants fed cow's milk mixtures providing less than 12 to 15 per cent of the calories in protein to deficiency of protein. Sweetened condensed milk which contains about 10 per cent of its calories in protein is frequently cited as an example of a feeding inadequate in protein. It is well known, however, that many modifications of cow's milk designed to resemble human milk, and consequently low in protein, are used for infant feeding without any evidences of impaired nutrition.

The nitrogen balances of infants fed a cow's milk mixture low in protein should afford an indication of the adequacy of the intake of protein. The present study was, therefore, undertaken to determine the retention of nitrogen of infants fed a cow's milk mixture providing about 10 per cent of the calories in protein. Sweetened condensed milk was used, but the results probably apply to other cow's milk modifications of similar protein content.

METHOD

The subjects of the experiments were five healthy infants ranging from four to seven months of age. Their nitrogen balances were determined first when given diluted sweetened condensed milk and then

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when fed an equal number of calories in the form of a cow's milk mixture providing about 15 per cent of the calories in protein. This consisted of unsweetened evaporated milk diluted with an equal volume of water to which was added sucrose to make up 6 per cent by weight of the total mixture. In addition, one infant was studied during a third period on a feeding of diluted evaporated milk without added sugar which supplied 20 per cent of the calories in protein. The percentage of distribution of calories of the feeding mixtures used is shown in Table I. Both the sweetened condensed milk and the evaporated milk mixtures were supplemented with 8 c.c. of cod liver oil and 30 c.c. of orange juice daily. The total calories fed were sufficient to allow normal gain of weight and ranged from 100 to 120 calories per kilogram. Since sweetened condensed milk mixtures are relatively low in calcium and phosphorus, the retentions of these elements were also determined in addition to the retention of nitrogen.

Each infant was fed the milk mixture to be studied for at least ten days before the balance determinations. Following this foreperiod, the infants were placed on metabolism frames permitting the quantitative collection of urine and feces. The metabolism periods were of seven

TABLE I

PERCENTAGE DISTRIBUTION OF CALORIES

	PROTEIN	FAT	CARBOHYDRATE
Sweetened condensed milk	10	25	65
Evaporated milk and 6 per cent sucrose	15	40	45
Evaporated milk	20	55	25
Breast milk	8	47	45

days each. Carmine red was used to mark the feces. Aliquots of the milk mixture fed were taken for analysis. The food, feces, and urine were analyzed for nitrogen by the Kjeldahl method, calcium by a modification of the McCrudden method,[4] and phosphorus by the gravimetric magnesium pyrophosphate method.[4] The accuracy of the urine collections was checked by the determination of creatinine in each twenty-four-hour specimen. During each period the variations in the daily creatinine excretion were less than 10 per cent of the average for the period. The gain in weight of the infants was also noted.

RESULTS

The experimental results are summarized in Table II. The data are expressed in terms of twenty-four-hour periods.

The rate of gain in weight was satisfactory in all of the experiments, ranging from 19 to 41 gm. per day, and was essentially the same during the periods of feeding with sweetened condensed milk and with evaporated milk.

In four of the five experiments the retentions of nitrogen during the periods of low protein feeding were approximately equal to the retentions obtained with the higher levels of protein. The constancy of retention of nitrogen is quite strikingly shown by the subject E. M., who retained the same amount of nitrogen when 10 per cent, 15 per cent or 20 per cent of the calories were provided in protein. One subject, H. B., showed a considerably greater retention of nitrogen during the evaporated milk period.

The sweetened condensed milk feedings supplied only about two-thirds as much calcium and phosphorus as the mixtures of evaporated milk and sucrose. Less calcium was retained during the periods of lower calcium intake except in one experiment. The retentions of phosphorus corresponded approximately to those expected from the calcium and nitrogen balances, i.e.,

$$\text{P retention} = \frac{\text{Ca retention}}{2} + \frac{\text{N retention}^{5}}{17.4}$$

TABLE II

DAILY NITROGEN, CALCIUM, AND PHOSPHORUS BALANCES

SUBJECT	AGE MO.	WEIGHT GM.	FEEDING	WT. GAIN GM.	N INT. GM.	N RET. GM.	CA INT. GM.	CA RET. GM.	P INT. GM.	P RET. GM.
W. K.	5	7,655	C.M.*	+35	2.92	+1.19	0.67	+0.22	0.55	+0.18
		9,600	E.M.+S.†	+36	4.46	+1.22	1.04	+0.33	0.82	+0.24
H. B.	7	7,915	C.M.	+39	2.65	+0.64	0.64	+0.24	0.52	+0.16
		8,670	E.M.+S.	+36	4.47	+1.12	1.04	+0.16	0.83	+0.17
T. B.	6	7,915	C.M.	+41	2.55	+0.96	0.57	+0.23	0.47	+0.17
		8,660	E.M.+S.	+40	4.38	+0.87	1.05	+0.32	0.79	+0.16
T. T.	5	7,260	C.M.	+23	2.60	+0.82	0.58	+0.17	0.47	+0.14
		7,720	E.M.+S.	+39	4.38	+0.82	1.05	+0.21	0.79	+0.14
E. M.	4	6,025	C.M.	+35	2.40	+0.82	0.56	+0.17	0.42	+0.13
		6,765	E.M.+S.	+19	4.02	+0.83	1.06	+0.20	0.73	+0.14
		7,455	E.M.‡	+29	5.63	+0.80	1.37	+0.24	1.02	+0.15

*C.M., diluted sweetened condensed milk.
†E.M. + S., diluted evaporated milk with 6 per cent sucrose.
‡E.M., diluted evaporated milk without added sucrose.

DISCUSSION

The failure of four of the subjects to show increased retention of nitrogen when the protein calories were increased from 10 to 15 per cent of the total calories indicates that the lower level of protein was sufficient to permit the maximum possible protein storage. The one subject, H. B., who showed less retention of nitrogen during the sweetened condensed milk period may not have been adjusted to the low protein feeding at the time the collection of urine and feces was started, since he showed increasing daily retentions of nitrogen during the period of low protein feeding. However, if this lower retention of 0.64 gm.

nitrogen daily be accepted, it still compares favorably with the reported retention of nitrogen of breast-fed infants. According to the literature, the daily nitrogen balance of healthy infants fed human milk averaged 0.56 gm.[6] Swanson[7] determined the retention of nitrogen of an infant fed human milk for a period of almost six months and found the average daily retention to be 0.54 gm. When sufficient calories are given, cow's milk mixtures which provide 10 per cent of the calories in protein apparently satisfy the infant's protein requirements. Increasing the protein in the diet above this level without increasing the calories does not result in increased storage of protein. The greater retention of nitrogen of artificially fed infants as compared with breast-fed infants, and especially of infants fed concentrated milk mixtures, may be associated with a higher intake of calories rather than of protein. Nelson[8] and Jeans and Stearns[9] found that the retentions of nitrogen of infants fed undiluted milk or evaporated milk mixtures were greater than those of infants fed diluted milk mixtures. The infants receiving the concentrated mixtures were given more calories as well as more protein than the infants receiving the diluted milk feedings.

No conclusions as to the protein minimum, meaning by this term, the lowest level of dietary protein permitting the maximum retention of protein, can be drawn from the present experiments. The fact that one subject showed a relatively low retention of nitrogen when given the 10 per cent protein feeding may indicate that this level is close to the minimum for infants fed cow's milk.

The nitrogen balances of the infants given sweetened condensed milk feedings do not support the commonly expressed belief that sweetened condensed milk is an inadequate food for infants because of its low content of protein. It is possible that the poor results of sweetened condensed milk feedings may have been due to deficiency of vitamins rather than of protein. This is in accord with the findings of De Sanctis and Craig[10] and Wolf and Sherwin[11] who reported normal growth and development in infants fed sweetened condensed milk supplemented with additional sources of vitamins C and D.

The lower intake of calcium and phosphorus during the periods of feeding with sweetened condensed milk was apparently associated with smaller retentions of these elements. This should not necessarily be interpreted as signifying that sweetened condensed milk is inadequate with respect to calcium and phosphorus. It has been observed many times that infants fed cow's milk supplemented with vitamin D show much greater retentions of calcium and phosphorus than do breast-fed infants. This is true even when the balance studies are carried out for long periods of time.[7, 12, 13, 14] Swanson[7] over a period of three months found that the daily retention of calcium of an infant fed human milk supplemented with cod liver oil averaged 0.08 gm. daily, whereas that of an infant fed a cow's milk mixture plus cod liver oil averaged 0.29 gm.

daily. Neither of these infants showed any evidences of rickets. Greater retentions of calcium and phosphorus can be obtained in infancy by increasing the amount of these elements in the diet, as the studies of Nelson[15] and Jeans and Stearns[9] show, but there is no evidence that this increased retention of calcium and phosphorus is necessary. Although the retentions of calcium and phosphorus of infants fed sweetened condensed milk supplemented with cod liver oil are less than those obtained with higher intakes of calcium and phosphorus, they are, nevertheless, considerably greater than those reported in normally growing breast-fed infants and are probably adequate.

SUMMARY

The retentions of nitrogen, calcium, and phosphorus of five infants ranging from four to seven months of age were determined when fed cow's milk mixtures providing 10, 15, and in one case 20 per cent of the calories in protein. The 10 per cent protein feeding consisted of diluted sweetened condensed milk. The feedings were all supplemented with orange juice and cod liver oil.

With an adequate intake of calories, the protein requirements of the infants were apparently satisfied when 10 per cent of the calories were provided by protein.

The retentions of calcium and phosphorus of infants fed sweetened condensed milk supplemented with cod liver oil were less than the retentions observed when the amounts of calcium and phosphorus in the diet were increased but were, nevertheless, considered sufficient to permit normal growth.

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RESPIRATORY FAILURE IN ACUTE EPIDEMIC POLIOMYELITIS

Late Results and Complications

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IN A PREVIOUS communication[1] we reported in detail our observations in forty-six patients with poliomyelitis treated in the Drinker respirators at the Willard Parker Hospital in 1931. We now present the follow-up data of these patients obtained over a period of four years after respirator treatment. During 1932 and 1933 seventeen additional patients with poliomyelitis were treated in the respirators at the Willard Parker Hospital. We shall summarize our observations in the entire group of sixty-three patients and discuss a frequent late pulmonary complication which often is not recognized.

ANALYSIS OF SIXTY-THREE CASES

Types of Patients Treated.—The patients were divided into two groups (spinal and bulbar), according to the type of respiratory paralysis present. The patients in the first group had paralysis of the diaphragm or the intercostal muscles* or both and were classified as spinal cases. Paralysis of the intercostal muscles was determined by watching the expansion of the chest during inspiration. The magnitude of expansion was more readily estimated by pressing firmly on the upper abdomen, thus diminishing the excursion of the diaphragm. Paralysis of the diaphragm was determined by observing the movement of the abdominal wall during inspiration. If there was no abdominal movement, or if the abdomen was drawn inward during inspiration, it indicated weakness or paralysis of the diaphragm. The involvement of the respiratory muscles was often unilateral. Fluoroscopy was sometimes used to corroborate the clinical impression.

The patients in the second group had involvement of the cranial nerves with apparent injury of the respiratory center and were classified as having bulbar lesions.† The diagnosis of injury to the respiratory center was made in patients with bulbar lesions, whose respirations were irregular in depth and rate at a time when the upper air passages

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*The diaphragm and intercostal muscles are not the only ones that function during inspiration. Some of the other muscles are the levators costarum, scaleni, sternocleido-mastoid, pectoralis minor and serratus posticus superior. These may also be paralyzed but are of minor importance.

†Bulbar is used in the broad sense. Although it is anatomically incorrect, it has become accepted usage to divide the more common lesions in poliomyelitis into spinal and bulbar. The latter includes the nuclei of the cranial nerves as well as the respiratory center.

were not obstructed (by mucus or saliva), and who did not have paralysis of the respiratory muscles.

There were several patients with paralysis of the intercostal muscles or diaphragm who also had paralysis of some cranial nerves. These patients were considered as having spinal lesions, so far as the respiratory paralysis was concerned. Similarly some patients with involvement of the respiratory center had paralysis of one or more extremities, but, so far as the respiratory paralysis was concerned, they were considered as having bulbar lesions.

When determining injury to the respiratory center, it is important to have the upper air passages free of mucus and saliva. An erroneous diagnosis of respiratory paralysis was made in at least two patients who were unable to swallow. The mucus and saliva which accumulated in the pharynx of these patients interfered with respiration. Each one received respirator treatment for several hours without improvement. After removal from the respirator and the institution of suitable treatment, they improved and finally made a complete recovery. Placing such patients in the respirator is likely to result in emphysema and aspiration pneumonia as Harper and Tennant[2] have pointed out. These patients are not included in the sixty-three cases under consideration in this paper.

Age and Sex.—The youngest patient treated was fourteen months of age and the oldest twenty-four years. There were four patients under three years of age, all of whom died. The distribution between the sexes showed nothing significant.

Time Factors.—There was apparently no correlation between the duration of the respiratory difficulty and the ultimate result. Some patients who were placed in the respirator shortly after the appearance of respiratory embarrassment died; whereas others, who had respiratory embarrassment for as long as nine days before treatment survived.

Differential Diagnosis.—Pneumonia, asthma, and other conditions are not infrequently erroneously diagnosed as respiratory paralysis due to poliomyelitis, and patients with these conditions are sent to the hospital for treatment. Gordon[3] found that seventeen cases of pneumonia were incorrectly diagnosed as poliomyelitis and sent to the Herman Kiefer Hospital during a time when the total number of patients admitted with poliomyelitis was 224. In 1933 nine patients with pneumonia were sent to the Willard Parker Hospital for treatment.[4] Probably many such errors in diagnosis could be avoided by obtaining a careful history and performing a thorough physical examination. We have never seen a patient with involvement of the respiratory muscles due to poliomyelitis who did not have, in addition, paralysis or paresis of some other muscles.

Pulmonary Complications.—Twenty-seven of the sixty-three patients treated in the respirators were discharged from the hospital. Twelve

TABLE I

ANALYSIS OF TWELVE DEATHS AFTER RESPIRATOR TREATMENT

CASE NO. HOSPITAL NO. AGE	TIME INTERVAL BETWEEN END OF OUR RESPIRATOR TREATMENT AND DEATH	ROENTGENOGRAM	TERMINAL ILLNESS, CLINICAL DIAGNOSIS, AND COURSE
1 4311 5 yr.	8 mo.	Massive atelectasis	Seven months after discharge patient had scarlet fever and varicella. During convalescence temperature rose, and patient became dyspneic. Clinical diagnosis of pneumonia was made. During next eight days patient became progressively worse and died. First roentgenogram showed atelectasis which was later complicated by a bilateral pneumonia.
2 4325 3 yr.	3 wk.	Massive atelectasis	Normal convalescence at an orthopedic hospital for 9 days; patient developed upper respiratory infection for 2 days and then suddenly became desperately ill with dyspnea and cyanosis. Clinical diagnosis was pneumonia, but roentgenogram showed a massive atelectasis of entire right lung. Patient died 20 hr. after onset of acute symptoms.
3 4751 13 yr.	2 yr.	Six months before fatal illness patient had massive atelectasis from which he recovered.	Patient had anorexia, cough, and fever at home for one week. Cough became worse, and patient vomited. Hoarseness and dyspnea developed. Examination at hospital revealed coarse moist râles in both lungs, diminished resonance and fremitus, and profuse nasal discharge. Temperature 101.4° F. The same night he became restless and cyanotic; pulse was feeble. Few hours later he was unconscious. He died 16 hr. after admission. Diagnosis was cardiovascular failure, pneumonia, and possibly pulmonary edema.
4 4925 6 yr.	6 wk. 2½ yr.		Patient was doing well at an orthopedic hospital for one month. Suddenly patient developed respiratory difficulty with cough and slight cyanosis. Moist râles were heard over entire chest. Temperature 100° F. Diagnosis of bronchial pneumonia was made. Respirator treatment and oxygen did not help. The following days the temperature was between 103 and 104° F. Condition became worse, and patient died five days after onset of acute symptoms.
5 4323 11 yr.	2½ yr.		Convalescence had been progressive. He developed a slight cold with cough, similar to condition he had on previous occasions. This time there was a more copious secretion of mucus. Temperature was normal. Suddenly he became dyspneic, cyanotic, and apprehensive. Coarse moist râles in both lungs, more at the apices, no dullness. Impression was pulmonary edema. He died 10 hr. after onset of acute symptoms.

TABLE I—CONT'D

CASE NO. HOSPITAL NO. AGE	TIME INTERVAL BETWEEN END OF OUR RESPIRATOR TREATMENT AND DEATH	ROENTGENOGRAM	TERMINAL ILLNESS, CLINICAL DIAGNOSIS, AND COURSE
6 4719 11 yr.	3½ mo.		Uneventful convalescence at Willard Parker Hospital for 3 weeks and another hospital for 2 months. Temperature 99° to 100° F., pulse 90 to 100, and respirations 20 to 26. Taken home against advice of attending physicians. Apparently well at home for 3 weeks. Then suddenly patient became ill, complained of headache, rapidly became stuporous, and developed difficulty in breathing and cyanosis. Three hours after onset admitted to Fordham Hospital as an emergency case. Impression was pneumonia and possibly relapse of poliomyelitis. Placed in respirator with some improvement in color. Stupor persisted, pulse poor, temperature 100° to 102° F. Patient died 25 hr. after admission. Unfortunately the case record and autopsy report could not be found.
7 5776 14 yr.	3 wk.		Patient discharged in satisfactory condition after 10 days in general hospital. The day the patient arrived home there was a sudden onset of dyspnea and cyanosis with rapid development of coma. There were distant breath sounds over both sides of chest but no râles. Temperature 103° F. In respirator 10 hr. without improvement; died 20 hr. after onset of acute symptoms.
8 4669 5 yr.	2 wk.		This patient was discharged from Willard Parker Hospital to another hospital for further respirator treatment in order to make room for more urgent cases. He was treated for 5 days more with improvement and removed from the respirator. The patient was taken home by the parents against the advice of his physicians. Three days later he was brought back as an emergency case with shallow, labored breathing and cyanosis. Breath sounds on the left side were diminished. Temperature 99° F. Diagnosis of possible pneumonia was made. There was some improvement, but after 2 days he suddenly became worse; marked dyspnea, cyanosis, and restlessness developed, but no elevation of temperature. He died 10 minutes after recurrence of acute symptoms.
9 5511 13 yr.	1½ yr.		Letter from mother states patient died of pneumonia at home.

TABLE I—CONT'D

CASE NO. HOSPITAL NO. AGE	TIME INTERVAL BETWEEN END OF OUR RESPIRATOR TREATMENT AND DEATH	ROENTGENOGRAM	TERMINAL ILLNESS, CLINICAL DIAGNOSIS, AND COURSE
10 5523 15 yr.	5 mo.		Letter from mother states patient died of pneumonia at home after an illness of 4 days. Oxygen administered without benefit.
11 5300 10 yr.	2½ yr.		Letter from mother states that patient died of pneumonia at home in Lenox, Mass., 24 hours after onset of acute symptoms.
12 5114 20 yr.	6 mo.		Patient had been convalescing nicely for 6 mo. at a general hospital. Died of agranulocytosis after administration of several doses of amidopyrine for abdominal pain.

of these twenty-seven patients who survived the respirator treatment in the hospital died at intervals of from two weeks* to two and one-half years afterward. The cause of death in these twelve patients is of considerable interest. All of them had residual paralysis of some of the respiratory muscles. One patient developed neutropenia following the administration of amidopyrine for several days. The fatal illness in the other eleven patients began with respiratory symptoms, and the clinical diagnosis in eight was pneumonia and in one, pulmonary edema. Roentgenograms were taken of the two remaining patients during their final illness, and in both a roentgenologic diagnosis of massive atelectasis was made. The clinical diagnosis in these two patients was pneumonia (Table I, Cases 1 and 2).

It is sometimes most difficult to differentiate clinically between massive atelectasis and pneumonia, even when one keeps in mind that either condition may be present. Although pneumonia may develop after respirator treatment, it is significant that in none of the patients in whom pneumonia was the final diagnosis was this confirmed by roentgenograms. We were able to obtain a fairly accurate description of the fatal illness in a few instances, and some of these closely simulated the sequence of events in cases of massive atelectasis (Table I, Cases 3 to 6). There was a history of an upper respiratory infection in some, with moderate ineffectual cough and rapidly progressing dyspnea. Cyanosis developed despite treatment in a respirator or the administration of oxygen by nasal catheter. There was usually a rise in temperature which varied from 2° to 6° Fahrenheit. The respiratory excursion was diminished on the affected side (sometimes obscured by the muscle paralysis),

*The patient who died after two weeks was removed from the hospital against the advice of the attending physicians.

and suppressed breath sounds with moist râles were heard over the involved area. The condition became progressively worse, and death occurred in from a few hours to several days.

Although massive atelectasis was a serious occurrence in our handicapped patients, it developed in some of them during, as well as after, respirator treatment without a fatal issue. Two patients had atelectasis of the right upper lobe while in the respirator. The diagnosis was made clinically and confirmed by roentgenograms. Three other patients developed massive atelectasis two weeks, four months, and two years after their treatment in the respirator and recovered.

Massive atelectasis is the result of a prolonged occlusion of the lumen of a large bronchus. Several factors were present in our patients which predisposed them to such an occurrence. There was an intercurrent upper respiratory infection which increased the production of mucus. All the patients were able to cough but with diminished force, because some of the respiratory muscles were still paralyzed. We believe that the ineffectual cough permitted mucus to accumulate in the tracheobronchial tree which, in some instances, was followed by the plugging of a bronchus. The air in the alveoli related to that bronchus was absorbed, and the result was massive atelectasis.

Pathology.—We shall consider briefly the pathologic conditions found in the lungs of patients who died during treatment in the respirator. Most of the pathologic material was examined by Dr. Lawrence W. Smith at the Willard Parker Hospital. Emphysema and focal areas of atelectasis (lobular) were found in all cases. A few patients not treated in the respirator showed atelectasis and emphysema but not to the same extent. Vascular engorgement, congestion, stretching of the elastic tissue fibers, and an alveolar exudate of serum and blood cells were frequently found in treated cases. When the chest was opened in one case, the lungs were partially collapsed due to a loss of the normal elasticity. Similar findings have been reported by others.[2-5]

Patients Suitable for Treatment in the Respirator.—Should every patient with poliomyelitis who experiences difficulty in breathing receive respirator treatment? Because this question is of great importance we shall discuss it in detail and state why our answer is in the negative. Respiratory difficulty in poliomyelitis may be caused by (1) paralysis of the respiratory center, (2) paralysis of the diaphragm or intercostal muscles, either separately or in combination, or (3) accumulation of saliva and mucus in the retropharynx in patients with inability to swallow.

We have not been successful in the treatment of patients having bulbar lesions with paralysis of the respiratory center. Discouraging results with similar cases have been reported by other authors.[2, 8] Whether

these patients die of respiratory paralysis, cardiovascular failure, toxemia, or some other condition is not clear. Possibly more of them would survive if the respirator was not used.

Patients with inability to swallow accumulate mucus and saliva in the retropharynx which may interfere with respiration. Aspiration of oral secretions or vomitus during normal or artificial respiration is a constant danger and may lead to atelectasis, emphysema, or pneumonia. If there is no respiratory paralysis, the patients will be able to breathe provided that the air passages are kept clear. Postural drainage, frequent use of a suction apparatus, parenteral administration of fluids, and no oral feeding for several days is the regime we have used for such patients.[9]

The most frequent cause of respiratory embarrassment in patients with poliomyelitis is due to spinal lesions which result in paralysis of the diaphragm or intercostal muscles. It is in this group that one finds patients suitable for respirator treatment. For patients with paralysis of one side of the diaphragm, or only some of the intercostal muscles, who do not have cyanosis or dyspnea, we do not advise respirator treatment. On the other hand, it has been suggested that the respirator should be used at the first sign of involvement of the respiratory muscles, in order to rest the injured nerve cells.[5] Unfortunately, at present, we do not know whether artificial respiration prevents stimulation of the nerve cells associated with respiration. The conditions produced by artificial respiration are not comparable to the immobilization of the paralyzed skeletal muscles of an extremity. A further analogy to skeletal muscles which is sometimes made does not necessarily apply to the respiratory muscles. The impression is that spontaneous breathing will stretch the weakened respiratory muscles, just as weakened skeletal muscles of an extremity are stretched by incorrect immobilization or during active motion by antagonistic muscles. There are functionally no antagonistic muscles to the diaphragm or intercostal muscles, and therefore stretching of the paralyzed muscles will not occur. Another point to be borne in mind is that pulmonary complications may occur in patients treated in the respirator. We have observed many patients with respiratory embarrassment due to poliomyelitis who were not treated with artificial respiration. As far as we know, none of these developed pulmonary complications similar to those described earlier in this paper. For these reasons a patient should be in a respirator only if he is unusually restless, fatigued, or dyspneic or has cyanosis which cannot be relieved by the administration of oxygen. For patients with slight or moderate respiratory distress we advise repeated small doses of sedatives and continued reassurance to make them more comfortable and enable them to rest.

Treatment.—We have described the care of the patient requiring respirator treatment in detail elsewhere[1] and shall make only a few

additional comments. It has been suggested that patients be placed in the respirator several hours each day during their convalescence, that is, after their respiratory function has returned sufficiently to enable them to breathe spontaneously.[6] We were able to do this with one patient, and the result was most encouraging. In the acute stage some of our patients were given convalescent serum and others received ephedrine intrathecally.[7] The small number so treated prevented a suitable evaluation of either form of therapy. Deaths occurred among patients who received serum in the preparalytic stage. Ephedrine sulphate administered in the paralytic stage seemed to benefit some patients, whereas in others it apparently had no effect.

RESULTS

Bulbar Cases.—All of the twelve patients with bulbar lesions and injury of the respiratory center died. Four of them died within twenty-four hours, and five others within three hours after being placed in the respirator.

TABLE II

SIXTY-THREE CASES TREATED IN RESPIRATORS. THE MORTALITY DURING TREATMENT AND THE TOTAL MORTALITY ACCORDING TO THE TYPE OF LESION AND THE YEAR OF TREATMENT

YEAR	TYPE OF LESION	NUMBER TREATED	DIED DURING RESPIRATOR TREATMENT		DIED AFTER DISCHARGE	TOTAL DEATHS	
			NUMBER	PER CENT		NUMBER	PER CENT
1931	Spinal	34	16	41	10	26	76
	Bulbar	12	12	100		12	100
1932-33	Spinal	17	8	41	2	10	59*
Total		63	36		12	48	

*Exclusion of the patient who died of neutropenia brings the total percentage of deaths to 53.

Spinal Cases.—Twenty-four of the fifty-one patients with spinal lesions died in the respirator, ten in less than twenty-four hours, and two in less than three hours. Obviously many of the patients arrived at the hospital too late for any possible benefit from artificial respiration, and this accounts in part for the high mortality which we had. Twenty-seven patients left the hospital alive.

The immediate mortality* among patients with respiratory embarrassment from spinal lesions due to poliomyelitis who have been treated in the Drinker respirator has been the same in each of the epidemic years under consideration (Table II). However, the ultimate mortality during comparable follow-up periods has decreased. Thus, during a period of two years after surviving their respirator treatment there were eight deaths among eighteen patients in the 1931 group (two more died after

*Immediate mortality includes those deaths which occurred during respirator treatment; ultimate mortality includes those deaths which occurred after respirator treatment and were possibly related to the respiratory paralysis or the treatment.

TABLE III

PATIENTS WHO SURVIVED. COMPARISON OF CONDITION OF PATIENTS WHEN RESPIRATOR TREATMENT WAS BEGUN WITH CONDITION AFTER TWO TO FOUR YEARS

CASE NO., HOSPITAL NO., AND AGE AT ONSET OF ILLNESS	CONDITION WHEN PLACED IN RESPIRATOR	DURATION OF FOLLOW-UP AND CONDITION WHEN REEXAMINED*
1 4912 8 yr.	Admitted on the third day of illness, acutely ill. Temperature 103.6° F.; nasal voice, difficulty in swallowing; neck and back stiff; paresis of neck muscles; hyperactive deep reflexes. On third day in hospital movements of diaphragm weak, slight respiratory difficulty. Following day restless, perspiring, cyanotic; paralysis of diaphragm. Placed in respirator for 18 hr., after which she was able to breathe spontaneously with only her intercostal muscles.	After 2 yr.: Active, normal child. No evidence of paralysis. Breathes normally; good cough. The child had made a complete recovery at the end of one year.
2 5000 8 yr.	Admitted on second day of illness with preparalytic poliomyelitis. Convalescent serum given intravenously. Third day in hospital paralysis of upper extremities; fourth day paresis of lower extremities; breathing almost entirely abdominal, voice weak. In respirator for 10 days.	After 3 yr. and 10 mo.: As active as any other child—runs, jumps, skates, rides a bicycle, and plays ball. Some atrophy and slight weakness of left deltoid but no limitation of motion. Left hand grip a little weaker than right. Slight weakness of abdominal muscles. Breathing both thoracic and abdominal. Has had no intercurrent illnesses.
3 20 8 yr.	Admitted on ninth day of illness. Had been in another hospital for 5 days where he became progressively worse. On admission he was cyanotic, gasping for air; had received artificial respiration in ambulance. Placed in respirator immediately after admission. Following day examination revealed weakness of neck and back muscles; quadriplegia; paralysis of upper intercostals. In respirator 3 days.	After 3 yr. and 8 mo.: Attended orthopedic clinic for a year, and last report stated that patient was discharged as completely recovered.
4 4791 9 yr.	Admitted on the fourth day of illness after a trip of 80 miles. Acutely ill; temperature 103° F.; nasal voice; difficulty in swallowing; slight left facial weakness; left side of palate weak. Unable to sit up; generalized flaccidity with rigid neck and back. No cyanosis or dyspnea. Following day there was more prostration and some restlessness. Beginning weak-	After 2 yr. and 3 mo.: Well-developed and active child; up and about. Slight weakness of left lower facial muscles and asymmetry of soft palate. Breathes, talks, and swallows normally except for slight huskiness of voice. All other muscles normal. Has had several attacks of bronchitis, some of which were prolonged.

*Nineteen patients were reexamined by one of us, the last examination after the time interval indicated. Patients 3 and 15 were not examined by us, but we obtained a report of their last examinations through the courtesy of the orthopedic hospital which they attended.

TABLE III—CONT'D

CASE NO., HOSPITAL NO., AND AGE AT ONSET OF ILLNESS	CONDITION WHEN PLACED IN RESPIRATOR	DURATION OF FOLLOW-UP AND CONDITION WHEN REEXAMINED[a]
4 4791 9 yr. Cont'd	ness of diaphragm and intercostal muscles. Slight cyanosis relieved by oxygen. Next day diaphragm paralyzed, and cyanosis persisted, therefore patient was placed in respirator. Had stormy course due to inability to swallow saliva and mucus. In respirator for 2 periods of 5 and 4 days, each with an intervening interval of 20 hr.	
5 5214 3 yr.	Delirious, dyspneic, no thoracic movement; suprasternal retractions, weak muscles of neck and back; paresis both lower extremities and of left upper. Placed in respirator 4 hr. after admission on the fourth day of illness. In respirator 14 days.	After 4 yr. and 3 mo.: Well-developed, alert child as active as any her age. Attends school. Examination shows weakness of left intercostals and muscles of left shoulder and arm with some atrophy. Slight scoliosis is present.
6 4830 12 yr.	Quadriplegia; weakness of neck and back muscles. Breathing with great difficulty using only diaphragm. Feeble voice, drowsy, perspiration, slight cyanosis. Used accessory muscles of respiration. Was in respirator 3 weeks. During respirator treatment developed massive atelectasis of right upper lobe.	After 4 yr.: Active alert boy. Attends high school—walks two miles to and from school each day. Uses upper extremities for all necessary movements, in spite of advanced atrophy of muscles of both arms. Has a marked scoliosis and atrophy of the upper intercostal muscles. No intercurrent infections.
7 5349 14 yr.	Quadriplegia, rigid neck. Shallow breathing, no thoracic and little abdominal movement; used accessory respiratory muscles; talked in a whisper; slight cyanosis. Placed in respirator on admission—the seventh day of his illness. In respirator 4 days.	After 3 yr. and 9 mo.: Walks well except for slight lag of left leg. Almost complete flaccid paralysis of right upper extremity. Atrophy of muscles of the right upper chest and shoulder. Scoliosis—patient wears brace. No difficulty in breathing but becomes tired after walking several blocks. Will attend high school next term. No intercurrent illnesses.
8 5392 10 yr.	Quadriplegia. Temperature 105° F.; feeble pulse; drowsy; face dusky; petechial rash; dilatation of alae nasi; barely audible voice; no movement of thorax. Convalescent serum had been administered on two successive days preceding admission. In respirator 3 weeks.	After 4 yr. and 3 mo.: Alert, cheerful boy, able to sit up in wheel chair. Can walk a little with aid of crutches. Writes; feeds and clothes himself. Tutor comes to home. Wears a body brace and one for foot drop. Right shoulder, arm, and forearm flaccid, some strength. Right lower extremity flaccid. Left side has some power. Body is thin due to muscle atrophy. Chest expansion fair, voice good. No intercurrent infections. Has had several orthopedic operations.

TABLE III—CONT'D

CASE NO., HOSPITAL NO., AND AGE AT ONSET OF ILLNESS	CONDITION WHEN PLACED IN RESPIRATOR	DURATION OF FOLLOW-UP AND CONDITION WHEN REEXAMINED
9 5056 12 yr.	Admitted on the second day of illness with paralysis of both lower extremities and paresis of both upper extremities. Neck and back stiff; abdominal reflexes absent. Acutely ill but without respiratory embarrassment. Following day quadriplegia and extensive intercostal paralysis; voice weak; color poor. Placed in respirator. Had a stormy course with prolonged periods of cyanosis in spite of oxygen. Later developed paralysis of diaphragm. For the first 20 days respirator could be stopped for only few minutes at a time. In respirator 7 wk.	After 2 yr.: Shoulder muscles weak but moves forearms and hands well. Feeds herself and is able to write and turn pages of books. Poor function and atrophy of muscles of lower extremities. Gets about in wheel chair. Some spinal curvature. Respirations mostly abdominal but she breathes easily, cough fair, voice normal. School subjects taught by visiting teacher. No intercurrent illnesses.
10 6459 5 yr.	Rapid shallow breathing due to weakness of thoracic muscles and diaphragm; voice good. Weak neck and back muscles. Paralysis of lower extremities and paresis of upper extremities; distended bladder. Twenty-two hours after admission (sixth day of illness) placed in respirator because of practically no movement of thorax, dilatation of alae nasi, perspiring, and color poor. In respirator 19 days.	After 3 yr. and 10 mo.: Shoulders weak; forearms and hands have good function. Feeds herself and turns pages of books. Paralysis of lower extremities—she wears a brace. Can sit up and stand a little. No difficulty in breathing; speaks clearly; cough is fairly loud; respirations are thoracic and abdominal; respiratory capacity is diminished. No intercurrent illness.
11 4304 8 yr.	Admitted on sixth day of illness with weak neck and back muscles. Paresis of lower extremities; absent abdominal reflexes. Two days later spread of paralysis involving intercostals. Following day he was apprehensive, voice weak, slight dyspnea, diminished intercostal movement; color good. Placed in respirator for 20 hr.	After 3 yr. and 10 mo.: Flaccid paralysis of lower extremities, shoulders weak, spinal curvature. Can sit up, feed himself, and turn pages of books. Chest well developed. Thoracic excursion during respiration is symmetrical but diminished. Cough is fairly loud. Several colds but not of long duration. Appendectomy under inhalation anesthesia 4 mo. ago. Uneventful recovery. During his early convalescence this patient had massive atelectasis.
12 4893 11 yr.	Admitted on sixth day of illness. Acutely ill, weakness of lower extremities, back and neck; abdominal and all deep reflexes absent. Following day weakness of both shoulders and intercostal muscles. Two days later quadriplegia, distended bladder. Shallow abdominal respirations, spoke only in a whisper; slight	After 2 yr.: Sits propped up in a wheel chair. Cannot walk but is able to stand with braces. Paralysis and atrophy of shoulder muscles. Fair function of forearms and hands; feeds himself and reads books. Poor function of lower extremities. Spine straight. Respirations mostly abdominal but breathes

TABLE III—CONT'D

CASE NO., HOSPITAL NO., AND AGE AT ONSET OF ILLNESS	CONDITION WHEN PLACED IN RESPIRATOR	DURATION OF FOLLOW-UP AND CONDITION WHEN REEXAMINED
12 4983 11 yr. Cont'd	cyanosis. In respirator 3 wk. Three months after discharge had massive atelectasis with convulsions, cyanosis, and stupor. Mental impairment persisted for several months.	easily. No illness during past year.
13 6158 7 yr.	Transferred from another hospital on tenth day of illness. Acutely ill, gasping for air, cyanotic, temperature 102.2° F. Quadriplegia, weak neck and back muscles. Paralysis of lower intercostals and diaphragm. Placed in respirator immediately and oxygen administered. This patient received prolonged respirator treatment (6 mo.) after he could breathe without artificial respiration. Was dependent on the respirator for 8 wk.	After 2 yr.: Fair function in right forearm and hand. Impaired function left lower and left upper extremities. Neck muscles strong. Able to remain in sitting position when so placed. Slight scoliosis present. Breathes normally and has a good cough. Slight atrophy of muscles of right upper chest and shoulder. No illness during past year. A bed patient.
14 4894 11 yr.	Admitted on fourth day of illness with weakness of upper extremities which progressed to paralysis on the next day. The following day there was weakness of the lower extremities and paralysis of the diaphragm. He was using the accessory muscles of respiration and was slightly cyanotic. Respirator treatment for 4 wk.	After 2 yr.: General condition good; is comfortable and happy. Normal respiratory function. Limited movement of left upper extremity. Paresis of right upper and both lower extremities except feet and forearm. Sits up unaided. Able to swim in pool. Patient stated he is gaining muscle strength in extremities. For the most part, a bed patient.
15 4556 10 yr.	Quadriplegia. Restless; shallow, rapid breathing due to weakness of intercostals and diaphragm. Placed in respirator immediately after admission on the sixth day of illness. In respirator 12 days.	After 2½ yr.: Marked weakness of all extremities with only traces of muscle power. Unable to support trunk; spinal curvature. A bed patient.

two and one-half years) compared to two deaths among nine patients in the 1932-1933 group. This decrease in the ultimate mortality, we believe, is due partly to greater familiarity in handling the respirators. An important factor is that since the epidemic of 1931 the incidence of poliomyelitis in New York City has diminished and the number of patients requiring respirator treatment has decreased permitting better care of the individual patient.

VALUE OF THE RESPIRATOR

The value of respirator treatment has been questioned by some because of the high mortality and because many of the survivors are seriously crippled. In a recent article[10] it was shown statistically that the mor-

tality in a group of patients treated in the respirator was higher than in a group of supposedly comparable patients not so treated. The material for this statistical comparison was obtained from the charts of cases in four of the contagious disease hospitals in New York City. The necessary data were transcribed from the hospital charts onto a prepared form. From these forms cases with respiratory embarrassment not treated in the Drinker respirator were selected as a control group for comparison with a group treated in the respirator. The inherent error which occurs when a large number of persons, some unfamiliar with the patients, abstract and transcribe data from hospital charts is obvious. In evaluating a form of therapy, especially in a disease as variable as poliomyelitis, it is essential to observe personally all the patients—treated patients as well as untreated controls.

During the last four years we have observed numerous patients with respiratory embarrassment who were not treated in the respirator. After careful study it was evident that in our untreated cases as a group the paralysis was not as extensive, nor the illness in general as severe, as in the cases treated in the respirator. Consequently, they could not be used as a control group for comparative analysis.

Some of our patients, who would have died without respirator treatment, have practically no residual paralysis today (Table III). Others are partially incapacitated but are able to attend school. Unfortunately, others are greatly handicapped in the use of their extremities. Since no one can foretell which patient with respiratory failure will regain the use of his extremities or trunk muscles, all properly selected patients should receive the benefit of treatment in the respirator.

COMMENT AND SUMMARY

Analysis of the results obtained in sixty-three cases treated in the Drinker respirator indicates that the proper selection of patients for treatment is necessary. This is of especial importance in epidemic periods, when the number of respirators available is usually less than the demand. We have found the respirator useful only in patients with paralysis of the respiratory muscles due to lesions in the spinal cord. The patients with injury of the respiratory center who were treated in the respirator all died. Such patients, as well as those with obstruction of the upper air passages due to the inability to swallow saliva, mucus, or vomitus, do better when treated by other methods.

Patients with spinal cord lesions which cause paralysis of the diaphragm or thoracic muscles and who have definite signs of respiratory difficulty should receive treatment in a respirator. On the other hand, patients with slight evidence of respiratory embarrassment without dyspnea or cyanosis should not be placed in a respirator. Our opinion is based on the present knowledge of the physiology of respiration, the pathologic pulmonary conditions found in patients after treatment in

the respirator, and the late pulmonary complications occurring in patients who survived the respirator treatment. However, when a patient has any involvement of the respiratory muscles or evidence of an ascending paralysis, he should be in a hospital near a respirator because there is no way of telling whether the condition will become worse.

Follow-up data were obtained in all twenty-seven patients who were discharged from the hospital. Some recovered use of their paralyzed muscles and are normally active children; others are handicapped but are able to get about; and several are bedridden. After leaving the hospital, eleven patients died from some pulmonary condition, but in only two of these were roentgenograms taken. These were the only two fatal cases in which a diagnosis of massive atelectasis was made. Clinically atelectasis is frequently mistaken for pneumonia, and in some of the nine patients in whom a diagnosis of pneumonia or pulmonary edema was made, the history strongly suggested the possibility of atelectasis. Massive atelectasis developed but was not fatal in five patients. Thus we have the occurrence of massive atelectasis in seven (and possibly in others) of the twenty-seven patients who survived their original respiratory paralysis.

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BACILLUS ACIDI LACTICI MENINGITIS IN A NEWBORN INFANT

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THIS case is reported because of its rarity. There are only four other reports of meningitis due to *Bacillus acidi lactici* in medical literature, two being in newborn infants, one in a premature infant one month old, and one in an adult. There are only five references to infections from this bacillus in any part of the body.

REPORT OF CASE

In order to discuss more thoroughly the possible portal of entry of infection in this case, it is essential to report the antepartum course of the mother.

M. P., married, aged twenty-seven years, para i, gravida iii, gave the significant past history: (1) acute cervical adenitis as a child; according to the patient, cultures from these glands revealed a colon bacillus; (2) one spontaneous abortion in 1932 in the second month; (3) one full-term baby born in 1933 in Italy. The delivery was spontaneous after a nontoxic course, and the birth weight was five pounds. This child died at the age of eighteen months with a diagnosis of encephalitis lethargica.

Antepartum Course.—The patient was first seen by one of us (L. L. M.) on Nov. 12, 1934. At this time the physical examination was negative excepting for a smoothly enlarged thyroid and sinus arrhythmia. The course of her pregnancy was uneventful until Feb. 18, 1935. She then developed an acute vaginitis with excoriation of the mucosa. Fresh preparations were negative for *Trichomonas vaginalis* and smears were negative for gonococci. Potassium permanganate douches (1:4,000) were prescribed and local treatment applied. The discharge was repeatedly studied and gram-negative bacilli were found in almost pure culture. As the leucorrhea persisted and as the case clinically simulated trichomoniasis, an insufflation of stovarsol was given on March 18, 1935. Approximately three minutes after the insufflation the patient fainted. She was placed on a table in Trendelenburg position, and her breathing became loud and stertorous. Rigidity ensued, and she went into a severe tonic spasm with marked carpopedal spasm. Cyanosis was intense; the pulse was imperceptible; breathing ceased; and she gradually receded into a state of asphyxia pallida and appeared lifeless. One cubic centimeter of adrenalin was injected intramuscularly, and artificial respiration was begun. In about three minutes she took a deep breath, and spontaneous respiration was soon reestablished. For an hour she appeared dazed but gradually recovered consciousness and was able to leave the office two hours after the seizure. The blood pressure was 102/64 prior to the insufflation and rose to 120/80 two hours later.

The next day (March 19, 1935) she began to have labor pains although her date of confinement was calculated as May 2, 1935. She was immediately taken to York Hospital where, after a labor of eight hours, she was delivered spontaneously of a five-pound girl. The infant cried immediately and appeared healthy for its size.

Read before the New York Academy of Medicine Section of Pediatrics, May 9, 1935.

The postpartum course was uneventful, and the patient left the hospital after an afebrile puerperium. The antepartum vaginitis did not recur. On May 10, 1935, a small erosion about the external os was noted, and four days later under sterile precautions this erosion, the cervical canal, and the vaginal walls were cultured. Endo's agar plates were sterile, but blood agar plates showed almost pure cultures of *Streptococcus hemolyticus*, an occasional *Staphylococcus albus hemolyticus*, and a few colonies of *Bacillus coli communis*.

Clinical Course.—One of us (J. D. C.) first examined the baby six hours after delivery and found her to be negative physically. She was placed on a formula consisting of powdered milk modified with lactose—one ounce of the mixture being given every two hours. The feedings were taken well by a Breck feeder. After four days the formula was concentrated and the feeding intervals lengthened. Her course was uneventful until the eighth day, and there was no vomiting at any time.

On the eighth day the child began having periods of sudden marked generalized cyanosis lasting from 15 to 90 seconds. Respirations during these attacks were reduced to an average of three to five per minute. The institution of oxygen and 5 per cent carbon dioxide immediately cleared the existing cyanosis. Physical examination during and between attacks was negative except for the cyanosis and the reduction in respiratory rate. The fontanel was at no time full; there were no pathologic neurologic findings and at no time was there an elevation of temperature. With the onset of these attacks the infant refused food and gavage was started. Still there was no vomiting. In the next sixteen hours there were eight similar seizures. The infant was moved to the Babies Hospital where she was placed in an oxygen tent and fed breast milk from a Breck feeder.

On the tenth day after twelve hours in the Babies Hospital, the last hour of which she had been out of the oxygen tent, the baby had had no cyanotic attacks, and the temperature and physical examination remained normal. Breathing was not apneic, and she took the feedings well. Throughout the eleventh day her condition remained the same.

Upon the morning of the twelfth day the baby had five attacks in four hours consisting of generalized blushing, screeching, and waving both arms and legs, the left more than the right.

Following these attacks she held her breath and became cyanotic. The fontanel for the first time was slightly full, and the heart and respirations were irregular. Lumbar puncture revealed thick yellow tenacious pus containing four-plus globulin and a gram-negative organism.

On the thirteenth day the child had many convulsions and was fed by a medicine dropper. A second spinal tap yielded pus again. The laboratory reported *Bacillus acidi lactici* from the spinal fluid obtained the day before.

On the fourteenth day the child was moribund and died late in the day. No intraspinal therapy was attempted.

An autopsy was performed fourteen and one-half hours postmortem. The anatomical diagnoses were as follows: acute pachymeningitis; acute ependymitis; acute purulent otitis media—right—*Streptococcus hemolyticus;* lobular pneumonia—right; accidental involution of thymus; angiomatoid nodules on tricuspid and mitral valves; patent foramen ovale; anomalous fissuration of lungs; azygos lobe; dilated cavum septi pellucidi and septi Vergal.

Final Autopsy Note.—A case of *Bacillus acidi lactici* meningitis in which the portal of entry could not be determined. Acute otitis media was considered at autopsy as a possible focus, but cultures and Gram stains of sections from the right middle ear demonstrated a streptococcus. The pneumonia, undoubtedly a terminal feature, was due to a gram-positive coccus morphologically a streptococcus.

COMMENT

Bacillus acidi lactici is a gram-negative bacillus belonging to the colon bacillus group. It is found in the intestinal canal and is considered to be a harmless saprophyte without pathogenic significance. It may be present in water and may be present in milk.[1]

Greenthal[2] reported a case of *Bacillus acidi lactici* meningitis occurring in a premature negro girl aged one month. Death occurred on the eighth day after the onset of symptoms, and at postmortem *Bacillus acidi lactici* was recovered from the exudate on the surface of the brain and from a purulent discharge from the right middle ear.

At a meeting of the American Pediatric Society Sherman[3] reported a fatal case of purulent meningitis in a newborn infant due to a gram-negative bacillus. The bacillus was not identified with any known pathogen. The description of the organism and its cultural characteristics undoubtedly classify it as *Bacillus acidi lactici,* and Neal[4] regarded it as such.

Ray[5] described a case in an adult, aged fifty-five years, with a positive blood culture of *Bacillus acidi lactici* and a positive culture of the spinal fluid on two occasions. At postmortem examination the organism was recovered from the viscera and from the brain.

Pasachoff[6] reported a case in a newborn infant in whom the symptoms started on the tenth day of life and death occurred thirteen days later.

Morphologically *Bacillus lactis aerogenes* is the most similar of all bacilli to *Bacillus acidi lactici;* however, the former can be readily differentiated by its ability to ferment saccharose. Meningitis due to *Bacillus lactis aerogenes* has been found in three instances.[7]

In analyzing more than 1,500 cases of meningitis seen by the Meningitis Division of the Research Laboratory of the Department of Health of New York City up to 1924 Neal[4] found only five cases due to the colon bacillus group, none of these due to the *Bacillus acidi lactici.* In 1934 in a group of 623 cases of meningitis other than those due to the meningococcus or *Bacillus tuberculosis,* she[8] found none due to *Bacillus acidi lactici.* The only other reference to infection from this bacillus in the literature is a report of two adult cases of acute bacterial endocarditis reported by Dickar.[9] Neither of these patients recovered.

Mode of Entry of Infection.—In view of the fact that the autopsy findings did not reveal the portal of entry, the following are necessarily merely interesting theories.

1. That the focus was a prenatal infection of the mother. Dandy and Blackfan[10] expressed belief that intrauterine meningitis is not infrequent and in many cases is an etiologic factor in the production of hydrocephalus. The fact that in our case the infant did well for the first eight days tends to rule out this possibility; however, one must

not forget the tonic spasm of the mother immediately preceding labor in regard to a low grade discharge in which, among others, gram-negative bacilli were found in almost pure culture.

2. Infection from the otitis media. The culture of streptococcus from the ear at autopsy eliminates this.

3. Infection through the lymphatics or by direct extension from contiguous foci in the nose or mouth may be possible; however *Bacillus acidi lactici* is not ordinarily an inhabitant of these areas at this early age.

4. Premature respirations with aspiration of contaminated liquor amnii through the eustachian tube might be considered as a portal of entry had the symptoms begun earlier.

5. Milk-borne infection might have been possible, but the food was not cultured.

The explanation may lie in the aforementioned theories, but we have not enough evidence to draw any definite conclusions.

Treatment.—In none of the cases reported nor in our case was intraspinal therapy attempted. If a case were diagnosed early enough and if the patient were in condition to stand the shock of intraspinal therapy a polyvalent *Bacillus coli* bacteriophage could be logically used.

SUMMARY

A case of meningitis due to *Bacillus acidi lactici* in a newborn infant is reported. Review of the literature shows that only four instances of meningitis due to this organism have been reported. Three were in newborn infants and one in an adult, and none survived. The possible portals of entry are considered.

We desire to thank Dr. Herbert Wilcox for his help and for allowing us to report this case. We also thank Dr. Martha Wollstein for her excellent autopsy report.

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INTERPRETATION OF ROUTINE BLOOD CULTURES IN YOUNG INFANTS

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IN A PREVIOUS report from this clinic, Dunham has shown that bacteremia in the first month of life is not a rare occurrence.[3] In the cases she studied, the mortality was high, and in many instances the mode of entry of the infection was not obvious, and the classic signs of sepsis were absent. As a result of these observations, the present investigation was undertaken in which blood cultures have been taken routinely in obscure illnesses of young infants as well as in cases of obvious infection. Postmortem cultures have been done regularly within twenty minutes of death. The findings in this study may help to answer certain questions concerning the practicability and value of routine blood cultures in this age period and the significance of positive cultures. The chief questions which arise have to do with the difficulty of taking blood and the frequency of contamination, the possibility of clinical recognition of cases of generalized infection, the prognostic significance of a positive blood culture, and the actual part played by infection in a given case.

In interpreting the results of these blood cultures, the term bacteremia has been applied only to cases in which a pathogenic organism was demonstrated either on two successive cultures or on broth and plate from one sample of blood. Postmortem blood cultures have been interpreted conservatively, not because of postmortem dissemination of organisms, which would be negligible within twenty minutes after death,[1] but because on its way to the heart the needle may pick up organisms from the lung. Accordingly, the postmortem culture has been accepted as the sole proof of bacteremia only when there are over 200 colonies in the 1 c.c. pour plate. *Staphylococcus albus* and *Streptococcus viridans* have been regarded as contaminants unless present in both broth and pour plate. There is no difficulty in recognizing the other common contaminants.

In the period from June 1, 1932, to Jan. 30, 1934, blood cultures were done on 114 infants not more than one month old. In 96 cases the blood cultures yielded nothing of significance. In 20 of these cases the only cultures were taken postmortem, and of these, 15 showed no growth, 4 showed staphylococcus, and 1 *Streptococcus viridans*. In the remaining 76 cases, 116 cultures were taken, all during life; 105 of these were sterile, staphylococci were found in 15, diphtheroids in 3, *Streptococcus viridans* in 2, and *B. sublitis* in 1. These figures illustrate the practicability of routine blood cultures in young infants and show

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that an agonal bacteremia is not invariable. There were only 2 deaths in the group of 76 cases just mentioned.

In 18 cases pathogenic organisms were found; death occurred in 16 of these, and in all 12 of those in which the criteria given above were fulfilled. In 3 of these 12, the only cultures were taken postmortem, but the other 9 cases illustrate the ominous prognostic significance of a positive blood culture. Evidently generalized infection was not the explanation of the symptoms which led to the taking of a blood culture on the 76 "negative" cases.

Brief histories of the 12 cases fulfilling all our criteria for "bacteremia" are given, and the principal clinical, pathologic, and bacteriologic findings are summarized in Table I. *Streptococcus hemolyticus* was the predominant organism in 5 cases, and *B. coli* in 2 cases.

TABLE I

IMPORTANT CLINICAL, ANATOMIC, AND BACTERIOLOGIC FINDINGS

PATIENT	LESIONS NOT DUE TO INFECTION	LESIONS DUE TO INFECTION*	BLOOD CULTURES
1		Erysipelas. Scrotal abscess (*Streptococcus hemolyticus*)	*Streptococcus hemolyticus*
2		Erysipelas, cellulitis, pelvic abscess, peritonitis (*Streptococcus hemolyticus*)	*Streptococcus hemolyticus* postmortem culture showed *Streptococcus hemolyticus* + *B. coli*
3		Erysipelas, peritonitis (*Streptococcus hemolyticus*)	*Streptococcus hemolyticus*
4	Hemangioma of mitral valve	Nonsuppurative encephalopathy,† pneumonia	*Streptococcus hemolyticus*
5	Mongolian idiot, imperforate anus, erythroblastosis fetalis	Cellulitis of abdomen and legs	*Streptococcus hemolyticus*
6	Mongolian idiot, hydroureter	Pyelonephritis (*B. coli*), endocarditis	*B. coli*
7	Extradural hematoma, atelectasis	Meningitis (*B. coli*)	*B. coli*
8	Prematurity, atelectasis, intraventricular hemorrhage	Laryngitis, bronchitis, focal pneumonia, nodules in liver and spleen	Organism unidentified
9		Meningoangiitis (organism unidentified), hemorrhagic encephalomyelitis, focal necrosis of liver and spleen	Same organism as in Case 8
10		Meningitis (pneumococcus Type V), otitis media	Pneumococcus Type V
11	Atelectasis		*Streptococcus viridans*
12		Purpura, meninococcemia	Meningococcus

*In most instances these lesions were probably due to the organism found in the blood stream. Cultures made from the actual lesions are given in this column in parentheses. Thus "Scrotal abscess *Str. hemolyticus*" indicates that streptococci were cultures from the abscess itself.

†It is not certain whether this lesion should be attributed to infection or to cerebral anoxemia.

An interesting organism, not previously identified, was recovered in 2 cases. It is a hemolytic gram-positive rod, apparently closely related to an organism isolated from hemorrhagic encephalitis of calves.[2, 4] *Streptococcus viridans*, pneumococcus type V, and meningococcus were obtained in one case each. In a number of instances the result of the blood culture was a surprise. Apparently routine blood cultures must be taken of sick infants if cases of generalized infection are not to be missed. In few of the cases given here was the pathway of infection obvious. The one item which stood out as a predisposing factor was the presence of grave congenital or other preexisting lesions. However, in 6 of the cases all the major pathologic changes seemed attributable to infection. In one instance in which green streptococci were recovered in large numbers, the organisms probably had little to do with the infant's death. In all other cases significant bacterial lesions were demonstrated.

CASE REPORTS

CASE 1.—I. B., circumcised twentieth day; twenty-third day, red area on thigh. Admission on twenty-sixth day with extensive erysipelas and several abscesses in scrotum. Death on twenty-eighth day, no autopsy. Culture of scrotal abscess, hemolytic streptococcus. Postmortem blood culture, 2,000 colonies hemolytic streptococcus in 1 c.c. pour plate.

CASE 2.—A. L., showed swelling of scrotum on twenty-sixth day. Admitted thirtieth day with extensive erysipelas. Blood culture, hemolytic streptococcus. Death on thirty-first day. Postmortem cultures from heart, umbilicus, scrotum, and peritoneum showed a mixture of hemolytic streptococcus and *B. coli*. Anatomic diagnosis: Cellulitis of periumbilical tissues and scrotum, desquamative dermatitis of trunk and legs, pelvic abscesses, serofibrinous peritonitis, and hemorrhage into intestinal wall and both adrenals. Subsidiary: Patent foramen ovale, multiple lymphangiectases of intestines, and fibrosis of pancreas.

CASE 3.—F. M., well until thirteenth day when abscess was noted in vulva. Admitted nineteenth day with widespread erysipelas. Grew rapidly worse, developed signs of peritonitis, died on twenty-second day. Postmortem cultures of blood and peritoneal fluid showed hemolytic streptococci.

CASE 4.—B., pale and drowsy at birth, with irregular respiration. Third day, fever, right facial palsy, spasticity of left arm. No fluid obtained on lumbar puncture. Antemortem and postmortem blood cultures showed hemolytic streptococcus. Death on fourth day. Anatomic diagnosis: Extensive necrobiosis, demyelinization, and glial proliferation in brain; confluent focal pneumonia (bilateral), pulmonary congestion, and hemorrhage. Subsidiary: Hemangioma of mitral valve.

CASE 5.—C., mongolian idiot, admitted to hospital on first day because of absence of anus, was deeply jaundiced. After repair operation, there was rapid development of cellulitis of legs and abdominal wall, although the site of operation looked normal. Many normoblasts in peripheral blood. Antemortem and postmortem blood cultures showed hemolytic streptococci. Death on third day. Autopsy. Anatomic diagnosis: (a) Cellulitis of abdomen and legs; congestion and hemorrhage in lungs, liver, testes, adrenals; jaundice. (b) Congenital anomaly of rectum; recent operation (repair of imperforate anus). Subsidiary: Patent ductus arteriosus.

CASE 6.—D. H., a mongolian idiot, developed diarrhea and dermatitis at seven days. On the tenth day a specimen of urine showed pus; on the seventeenth day a blood culture showed *B. coli*. The diarrhea continued; fever developed in the fifth week, and death occurred on the thirty-ninth day. Autopsy. Anatomic diagnosis:

Pyelonephritis (bilateral), hydroureter (bilateral); acute mitral endocarditis. Subsidiary: Mongolian idiocy.

CASE 7.—D., a full-term infant, delivered by version and extraction, seemed well until the fourth day, when she became feverish. On the sixth day the temperature was 39° C., and the fontanel was bulging; the child died rather suddenly. Postmortem cerebrospinal fluid showed *B. coli* on smear; blood and cerebrospinal fluid cultures, *B. coli*. Autopsy. Anatomic diagnosis: Purulent meningitis, pulmonary atelectasis, extradural hematoma (right temporal). Subsidiary: Patent ductus arteriosus, foramen ovale, and bicornate uterus.

CASE 8.—C. A. M., born with cord around neck, admitted first day with cyanosis, irregular respiration, nasal discharge, coarse râles, impaired percussion note on left. Weight 2,175 gm. Death one-half hour after admission. Postmortem blod culture showed a hemolytic gram-positive bacillus, as described in the report by Burn. Autopsy. Anatomic diagnosis: Acute laryngitis and bronchitis, focal pneumonia (bilateral), pulmonary atelectasis and emphysema (bilateral), petechiae in pleura, focal proliferative nodules in liver and spleen.

CASE 9.—M. D., developed diarrhea on sixth day; ninth day feverish, refused feeding, admitted to hospital. Weight 3,120 gm.; temperature 101.8° F. Child was drowsy and spleen palpable. On the tenth day blood culture showed an organism identical with that found in Case 8. The child became increasingly drowsy, and meningeal signs appeared. No fluid obtained in lumbar puncture. Autopsy. The organism found on blood culture was demonstrated in the meninges both by culture and smear. Anatomic diagnosis: Suppurative meningoangiitis, suppurative hemorrhagic encephalitis and myelitis, cerebellar pressure cone, focal necrosis, and hemorrhage in liver and spleen.

CASE 10.—D. V., full-term infant, developed "heavy breathing" on the eighth day. On the tenth day he had a convulsion and was brought to the hospital. Temperature 39.6° F.; respirations labored, fontanel bulging; both ears full. Cerebrospinal fluid showed innumerable pneumococci (type V). Death on twelfth day. No autopsy.

CASE 11.—M. M., mother had a convulsion after forty-eight hours of labor; the cervix was dilated manually and the infant delivered by high forceps. The child was cyanotic, with irregular respirations, much mucus, bilateral atelectasis, and facial palsy. Death on first day. No autopsy. Postmortem blood and spinal fluid cultures revealed *Streptococcus viridans* in large numbers.

CASE 12.—M. N., had a "cold" on the twentieth day. On the twenty-sixth day he developed fever and diarrhea. The next day there was an extensive pupuric eruption, and child was brought to hospital. Blood smears showed intracellular diplococci. Meningococci were cultured from the blood, nose and throat. Cerebrospinal fluid 45 cells, all lymphocytes, Pandy 2+, culture, no growth. The child died shortly after admission.

CONCLUSIONS

1. The experience recorded here indicates that blood culture is a practical and useful diagnostic procedure during the first month of life.

2. The course of some of the cases cited is rather bizarre. Nevertheless, a positive blood culture in a young infant indicates a bad prognosis, and in most instances the rôle of the organism is not merely passive.

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EDEMA IN INFANCY AND CHILDHOOD AS AN EXPRESSION OF CHRONIC DIETARY INSUFFICIENCY

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THE epidemic occurrence of generalized edema in people suffering from famine following the World War served to focus attention on dietary deficiency as a cause of the condition. This type of edema has been produced experimentally in animals and has been extensively studied in both experimental and clinical subjects. It has been found to be characterized by hypoproteinemia and to result when the diet for a long time is deficient in protein and caloric value and high in water and salt content.

At present except in districts where famine is endemic, it is unusual to see more than occasional isolated instances of the sort of generalized edema originally described. The edema occurs in cachectic individuals or is seen in association with some chronic disease of the gastrointestinal tract. During the nine years that the authors have worked in Tennessee they have been impressed by the occurence of edema in children who were not extremely malnourished and who were not critically ill. The children were of families in a poor economic status and were those who presented themselves to our clinic for treatment. Occasionally there was no disease found other than malnutrition. More frequently the edema was found in patients with diarrhea or dysentery or some parenteral infection. At first these cases were observed and treated without making chemical studies of the blood. An occasional determination of total serum protein was made and the level found considerably reduced. Youmans'[1] study showed that nutritional edema was endemic in the medical out-patient group of this hospital. It seemed probable that the local dietary habits, poor economic status, and the prevalence of diarrhea were combining to make edema of nutritional origin a fairly common occurrence among the children as well as the adults. We studied therefore, the serum proteins on all cases of edema which we saw. The results of the studies on patients in whom there was neither cardiac nor renal disease are presented in this paper.

LITERATURE

No attempt will be made to review all of the scattered and voluminous literature on nutritional edema. Maver[2] gave an interesting description of the condition which was prevalent in parts of Europe following the

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World War. Ling[3] and Weech and Ling[4] investigated more fully a similar condition in patients from famine districts of China. By the time their investigation was made, deficiency of protein in the diet and decreased protein content of the blood serum were recognized as important factors in the production of edema.[5, 6] In the study of eighteen patients with generalized edema Weech and Ling[4] found that the serum proteins were invariably much reduced. Later work[7, 8] emphasized the greater importance of albumin as compared to globulin in maintaining a normal colloidal osmotic pressure in blood serum to regulate the fluid equilibrium between blood and tissues. When serum proteins are reduced as a result of dietary insufficiency, the loss is mainly in the more important albumin fraction.[9]

Most of the work on serum proteins reported in the literature has been done on the serum of adults or of experimental animals. It has been shown, however, that infants have a lower level of serum protein with a higher percentage of the total in the form of albumin than is true of older children.[10] It is generally agreed that at about two years of age, or when the diet becomes a general one, the serum proteins of children reach approximately the levels found in normal adults.[11-13]

Pediatric literature contains many scattered statements and figures indicating that acute and chronic infections in general, as well as various types of diarrhea, tend to lower the serum proteins, mostly at the expense of the albumin fraction. Webb[14] concluded that malnutrition in itself had no effect on the level of serum proteins in children although he found a slight reduction in certain acute and chronic infections. Davison[15] mentions the common occurrence of edema as a complication in protracted cases of dysentery while Fröhlich and Gozsy[16] emphasize the decrease in the albumin fraction in this disease. Some investigators[13] have noted a decrease in serum albumin in scurvy while others have failed to find such a change.[17] Although figures for serum proteins are generally not given, the nutritional disturbance associated with celiac disease has been described as frequently complicated by edema which is considered similar to war edema.[18, 19]

The results of many studies are confusing because the attempt is made to associate changes in serum protein with a given disease irrespective of the state of nutrition or degree of hydration of the patients studied. The use of a wide variety of analytical methods has added further to the confusion. The literature as a whole is singularly lacking in any extensive study of the relation of serum proteins to malnutrition and edema in children.

METHODS

In the work which we shall present here serum proteins were determined by the micro-Kjeldahl method. All determinations were run in duplicate. Total protein was determined on 1 c.c. of a 1:10 dilution of serum representing 0.1 c.c. of the original serum. The phosphoric-sulphuric-persulphate digestion described by Van

Slyke[20] was used. The nitrogen present was determined by distillation into 10 c.c. of N/50 HCl followed by titration with N/50 NaOH from an accurate buret. When sufficient material was available the nonprotein nitrogen was determined by the Folin-Wu procedure[21] and the value subtracted from the figure for total nitrogen obtained by the Kjeldahl method. In some instances the figures for total nitrogen were arbitrarily corrected by assuming the average value of 30 mg. of nonprotein nitrogen per 100 c.c. The protein nitrogen was converted to protein by the generally accepted factor 6.25.

The albumin and globulin were separated by Howe's method[22] of salting out globulin with sodium sulphate. The albumin nitrogen was determined in aliquots of the filtrate, corrected for N.P.N., and the nitrogen figure converted to protein as in the case of total protein. Globulin was invariably calculated by difference.

OBSERVATIONS OF NUTRITIONAL EDEMA

Over a period of nine years we have collected forty-one cases of edema in which a thorough study of the patient revealed no evidence of cardiac or renal involvement. Sometimes the edema was confined to the feet and legs, but there were several instances of generalized anasarca. The condition was observed in children from four months to nine years of age. Five children of the group had no demonstrable disease other than generalized edema; nine either had, or were convalescent from, bacillary dysentery; ten had diarrhea with stools not typical of dysentery; three had pneumonia; two were diagnosed as having celiac disease; three showed evidence of scurvy. There was one case each in which edema complicated pellagra, typhoid fever, tuberculous enteritis, diabetes, and a common cold. Four children had histories of repeated infections.

The previous diet was known to be good in three cases: the child with tuberculous enteritis, a child with diarrhea, and one with a history of multiple infections. In most of the other instances the diet offered was grossly deficient or there had been a long period when the appetite was poor. Breast feeding had been continued long after the supply of milk was sufficient, and supplementary foods had not been offered or consisted of gravy, biscuits, corn bread, cereal and potatoes. The older children ate only potatoes, corn bread, turnip greens, and beans. In many instances the food was offered with no regularity, and no attempt was made to teach the child to eat or to see that he received an adequate amount of food. The child's apparent preference coupled with what was convenient was the only guide to the diet. Supplementary vitamins were almost never given. Occasionally the dietary history as obtained sounded far better than the condition of either the child or the mother made credible.

From our total of forty-one cases we are presenting in Table I twenty-six in which studies of the various fractions of serum protein were made. No case is included in which there was found more evidence of renal involvement than a slight elevation of N.P.N. or a transient trace of albumin in the urine, following a period of low fluid intake. A few

TABLE I

CLINICAL AND CHEMICAL DATA ON TWENTY-SIX CHILDREN WITH EDEMA

CASE	AGE	WEIGHT LB.	WEIGHT OZ.	HEMOGLOBIN GM.	FEEDING	HISTORY AND DURATION OF DISEASE	EDEMA	PERCENTAGE OF SERUM PROTEIN		
								TOTAL	ALBUMIN	GLOBULIN
1	6 yr.	26	0	10.2	Breast fed 2 years. Since then diet mostly of fat meat and corn bread.	Sickly all her life. Pellagra and edema for 6 months.	General	5.0	2.9	2.1
2	2 yr.	16	15	9.1	Breast fed 1 year. No regular meals at present. Diet mostly soup and milk.	Poor health for 1 year. Edema for 7 months. Scurvy, general avitaminosis.	General	4.3	1.8	2.5
3	9 mo.	15	8	11.0	Breast fed. Cereal, bananas, and vegetables since 5 months.	Well first 6 months. Tuberculous enteritis.	Extremities	5.9	2.9	3.0
4	6 mo.	12	9	3.3	Breast fed 4 months. Various whole-milk formulas and lactogen since.	Acute G.I. indigestion 2 weeks. Severe secondary anemia.	Extremities	5.3	3.8	1.5
5	19 mo.	14	4	9.8	Breast fed, with added cereal, crackers and bread.	Had fever 3 months before and developed edema and diarrhea.	General	4.4	2.4	2.0
6	19 mo.	19	4	7.5	Cereal, vegetables, meat, fruit, milk, eggs.	Diarrhea and vomiting 4 weeks; edema 1 week.	General	4.6	2.7	1.9
7	2 yr.	25	6	8.1	Details unknown.	No disease. Edema 3 days.	Face, ascites	6.1	3.8	2.3
8	1 yr.	18	4	6.0	Breast fed. No supplementary food.	History of multiple infections.	Slight	5.3	3.5	1.7

TABLE I—CONT'D

CASE	AGE	WEIGHT LB.	WEIGHT OZ.	HEMOGLOBIN GM.	FEEDING	HISTORY AND DURATION OF DISEASE	EDEMA	PERCENTAGE OF SERUM PROTEIN		
								TOTAL	ALBUMIN	GLOBULIN
9	4 yr.	26	7	10.2	Diet of turnip greens, potatoes, and ham sandwiches.	Multiple infections for 5 months.	General	4.4	2.4	2.0
10	4 mo.	7	8	9.2	Breast fed 2 months. Then rice water, white of egg, and Imperial Granum.	Diarrhea 2 weeks. Intermittent edema all his life.	Marked, general	3.7	2.4	1.3
11	2 yr.	18	2	12.0	Breast fed with added cow's milk. No other food.	Diarrhea 3 months. Edema for some time.	Mild	5.1	3.2	1.9
12	19 mo.	16	6	9.0	Breast fed, with added buttermilk, vegetables, cereal, and fruit for last 7 months.	Diarrhea 3 weeks. Edema 3 weeks.	Marked, general	3.1	1.8	1.3
13	21 mo.	14	8	12.8	Family very poor. Very little food available.	Vomiting and diarrhea 2 weeks	Moderate, general	6.3	3.4	2.8
14	2 yr.	26	4	9.6	Breast fed 10 months. Since then chiefly potatoes, some fat meat, and apples.	Bronchopneumonia 3 days	General	3.5	2.4	1.1
15	2 yr.	13	1	8.8	Breast fed. Meat, egg, vegetables and milk for past year.	Diarrhea 1 month	Mild, of feet	4.7	1.9	2.8
16	6 mo.	15	6	4.6	Dilute skim-milk formula.	Diarrhea 1 month	Moderate, general	4.3	3.2	1.1

TABLE I—CONT'D

CASE	AGE	WEIGHT LB.	WEIGHT OZ.	HEMOGLOBIN GM.	FEEDING	HISTORY AND DURATION OF DISEASE	EDEMA	PERCENTAGE OF SERUM PROTEIN		
								TOTAL	ALBUMIN	GLOBULIN
17	19 mo.	14	11	8.9	Breast fed 14 months. "Regular diet" since.	Dysentery 5 weeks	Extremities	4.3	2.8	1.5
18	2 yr.	24	8	7.5	No details known.	Dysentery 8 months	Mild	4.7	3.4	1.3
19	14 mo.	14	10	11.4	Breast fed 13 months. Rice water, milk, and orange juice since.	Dysentery 2 months	Moderate, general	4.0	2.5	1.5
20	11 mo.	13	8	10.8	Breast fed 8 months. Since then oatmeal, pot-liquor, potatoes, gravy, and bread. No milk.	Diarrhea 1 month previously. Edema since that time.	Marked, general	4.8	2.1	2.7
21	2½ yr.	16	15	8.2	"Boarded out." Apparently starved for long time.	Starvation. Scurvy (?) Beriberi.	Marked, general	3.5	1.2	2.3
22	9 mo.	19	2	10.5	Whole milk and cereal.	Multiple infections all his life.	Mild, extremities	4.8	2.9	1.9
23	2 yr.	26	8	8.6	Breast fed 1 year. Then meat, bread, potatoes, vegetables, and milk.	Pneumonia. Lung abscess 4 weeks.	Marked, extremities	6.4	2.7	3.7
24	2 yr.	23	8	--	Breast fed 10 months. Mostly beans since.	Dysentery 2 weeks.	Marked, extremities	5.3	3.5	1.8
25	5½ yr.	21	12	13.2	On celiac diet 4 months. On general diet 1 month.	Severe diarrhea. Celiac disease.	Marked, extremities	2.8	1.4	1.4
26	9 yr.	34	8	8.6	Poor "general diet."	Celiac disease.	Extremities	3.5	1.9	1.6

children had been reduced to a state of cachexia by prolonged starvation or disease; two had celiac disease; one had no apparent disease. The majority were children who were poorly developed and undernourished but not critically ill, in whom a mild, acute or chronic diarrhea apparently brought out a latent edema. The levels of hemoglobin observed in the group of children give further evidence of their poor nutritional state. The photograph (Fig. 1) illustrates a typical case.

From Table I it is apparent that in every case the levels of total

Fig. 1.—Photograph of child presenting a typical picture of nutritional edema.

protein and serum albumin are lower than any generally accepted range of normals. The most marked reduction is in the albumin fraction. Occasionally the globulin is reduced but in a majority of instances is normal or increased above the average.

In order to bring out more clearly the variation of these figures from the normal the data are presented graphically in Fig. 2. The cases are divided into two groups, the figures for the children under two years of age being charted separately from those of the older group. Each horizontal space represents an individual. The albumin fractions are

arranged in ascending order of magnitude. Under each figure for albumin is charted the level of globulin and total protein of the same serum. The horizontal dotted lines drawn across the charts represent the normal level of the various types of protein for the two age groups. These normal levels are, of course, only approximate but are drawn at the average normal level as determined by our work to be published in

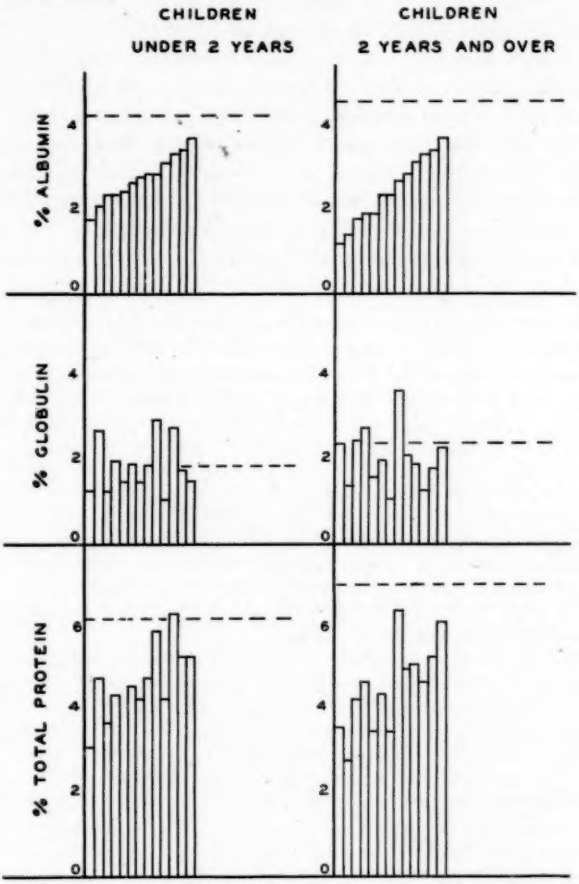

Fig. 2.—Graphic representation of levels of total protein, albumin and globulin of patients with edema. Dotted line indicates approximate normal level.

another paper. Our average normal is about the same as that published by other investigators.

In most instances treatment of the primary disease together with a high protein diet and transfusions of blood, when necessary, brought about a prompt reduction of edema followed by a gain in real weight and recovery. Determinations of serum proteins during the recovery

period showed a gradual increase to normal levels. In one instance, Case 21 in Table I, the circulatory collapse was so marked on admission and the serum albumin was so low that acacia solution was given intravenously in order to restore a more efficient oncotic pressure to the blood more rapidly than could be accomplished by other means. Sometimes the nature of the primary disease precluded any real improvement, or death resulted from intercurrent infection. In cases in which the edema was associated with the nonspecific type of diarrhea, it was interesting to note that as the serum proteins were raised to a more normal level and the edema disappeared, the diarrhea also subsided. This observation throws some doubt on which is primary and which secondary when nonspecific diarrhea and nutritional edema occur together in infants and children.

The two following protocols are included to show more in detail the course of recovery and restoration of normal serum proteins in two children who responded rapidly to treatment.

CASE 2.—(Table I.) R. L. G., white, female, aged two years, entered the hospital Oct. 3, 1934, with the complaint of being "swollen all over." The child had been breast fed for one year without supplementary foods or cod liver oil or orange juice. Since weaning she had received no regular meals but had nibbled at food throughout the day. Her diet consisted of soup, gravy, bread, potatoes, and salt meat with a little milk occasionally. Recently she had received large quantities of a tea made of watermelon and broom corn seeds. There had been no illnesses other than the present condition. Seven months before admission the feet and ankles began to swell and generalized edema gradually developed. The edema was intermittent but never was absent for more than a few days. Periods of anuria had occurred sometimes lasting as long as twenty-four hours. There had been no other urinary symptoms. Physical examination showed an undernourished, underdeveloped, pale child with marked edema of the legs, arms, and face. The serum proteins on admission were total protein, 4.3 per cent; serum albumin, 1.8 per cent; and serum globulin, 2.5 per cent. The urine was entirely negative.

The child was placed on a high protein diet which she ate well. In addition, a transfusion of 170 c.c. of blood was given. She lost two pounds during the first five days in the hospital; the edema disappeared; and a mild diarrhea, which had been present, subsided. Five days after admission, on Oct. 8, 1933, the serum proteins were: total protein, 4.9 per cent; albumin, 2.0 per cent; and globulin, 2.8 per cent. The child continued to eat well and to gain weight.

On Oct. 18, 1934, the serum proteins had risen to total protein, 6.7 per cent; albumin, 3.4 per cent; and globulin, 3.3 per cent. The child has been followed in the out-patient department and on an adequate diet has continued to do well. There has been no reappearance of edema.

CASE 6.—(Table I.) C. H. G., white, male, aged nineteen months, entered the hospital Oct. 28, 1930, with the complaint of diarrhea and vomiting of one month's duration. The child was supposed to have been well fed on a diet of cereals, bacon, fruit, vegetables, and milk, with an occasional egg, but the appetite had been very poor since the onset of the present illness. There was well-marked edema of the feet and legs. The serum proteins on admission were total protein, 4.6 per cent; albumin, 2.7 per cent; and globulin, 1.9 per cent. The urine was normal.

The child was put on a diet of whole milk for the first day or two and then on a regular soft diet which is moderately high in protein. The edema disappeared

during the first four days in the hospital. There was a weight loss of 1.5 pounds during this period and then the child began to gain. On Nov. 5, 1930, eight days after admission, the serum proteins were total protein, 6.0 per cent; albumin, 3.9 per cent; and globulin, 2.1 per cent. The patient gained 3 pounds in about two weeks in the hospital and has done very well since.

DISCUSSION AND SUMMARY

This study shows that generalized edema of neither cardiac nor renal origin may occur fairly often in infancy and childhood. This type of edema is most characteristically associated with malnutrition. The poor state of nutrition may result from chronic gastrointestinal disturbances, such as celiac disease, protracted dysentery, or tuberculous enteritis. Repeated or prolonged infection may also be a factor in its production. In the dispensary group in this locality the most common underlying cause of this type of edema is a diet which is grossly inadequate in total calories and in protein, either because of ignorance on the part of the parents or because of economic stress. A common factor in the condition, whatever the cause, is a marked decrease of serum protein, especially of the albumin fraction. Unless the primary disease is of a nature to preclude recovery, treatment with an adequate diet, sometimes supplemented by transfusions of blood, results in a restoration of normal serum proteins and a prompt reduction of the edema.

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THE OCCURRENCE OF MODERATELY REDUCED SERUM ALBUMIN IN FIVE HUNDRED CHILDREN IN A SOUTHERN CLINIC

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IN ANOTHER communication[1] we reported the occurrence of edema of neither cardiac nor renal origin in our group of clinic patients. Every instance of edema was associated with a marked reduction of plasma protein, especially of the albumin fraction. The hypoproteinemia was due primarily to malnutrition, although in some instances acute or chronic infections and gastrointestinal disease were undoubtedly contributory factors.

During the same interval that these observations were made, we noticed that many children who entered the hospital with acute diseases tended to develop edema very easily when moderate amounts of parenteral fluids were given. It seemed possible that many of the children in the clinic group, when they were apparently well, might have milder degrees of the same nutritional deficiency which had led to outspoken edema in the instances already reported. If such were the case, the nutritional disturbance would be analogous to subclinical vitamin deficiency. We therefore determined the serum protein levels of 500 children who came to our clinic. For comparison with these results a smaller group of well children of various ages who were known to be on adequate diets were similarly studied. The results of the studies are presented in this paper.

Our clinic is limited to children whose parents are unable to pay a private physician. The ratio of white to colored patients is about three to one. The infants who are fed under our supervision or that of one of the well baby clinics are usually well nourished. There are also many well-fed older children, but undersized and poorly nourished individuals are common. During the period of this investigation many of the families were out of work and supported by relief. Although the amount of money received by the families on relief was usually low, sometimes not more than three dollars a week for a family of four, often as much was spent for food as when the parents were employed. The depression undoubtedly contributed somewhat to the inadequacy of the food of many of the patients, but a more prolonged poor economic status and the dietary habits of the community are probably more important factors. Both older children and infants are often fed similarly to the children

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with nutritional edema whose cases were reported in our first paper. The dietary, as Youmans[2] has described for adults with edema, is often inadequate in protein and in total calories.

The blood for serum protein determinations on both normal and clinic children was taken without regard to activity or the interval after a meal. No rest period before the sample was taken was given to the older children who were well enough to walk into the clinic. The smaller infants and the sick children had, for the most part, been in a recumbent position for some time before the sample was taken. We realize that a uniform procedure under basal conditions would have given us more exactly comparable figures, but facilites were not available for such a study. All determinations of serum protein were made by the micro-Kjeldahl method as described in the preceding paper.[1]

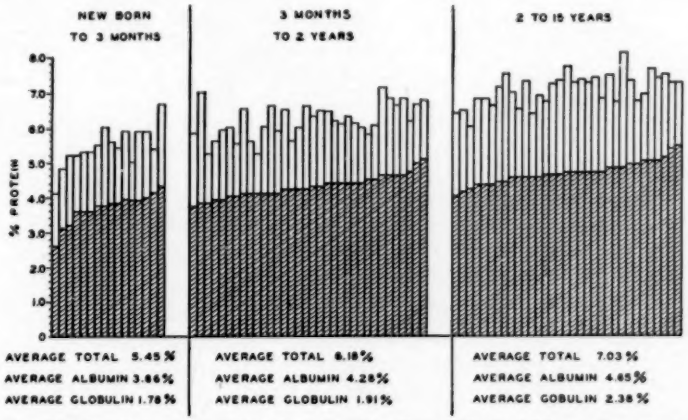

Fig. 1.—Levels of serum proteins in normal well-nourished children of various age groups.

SERUM PROTEIN LEVELS OF NORMAL WELL-NOURISHED CHILDREN

In order to evaluate the results obtained in the clinic group it was necessary to study the serum proteins of healthy, well-fed children throughout the range of pediatric age by the same chemical methods and under the same conditions. We found, as has already been shown by others, that small infants have a low concentration of serum proteins and that the level gradually rises as the child grows older, to reach the adult level at about two years of age. After two years no consistent variations were found. We therefore divided the normal children into three age groups: (1) newborn to three months; (2) three months to two years; (3) two to fifteen years. The results obtained are presented graphically in Fig. 1. Each horizontal space represents an individual. The height of the column represents the total serum protein, the crosshatched portion the albumin, and the clear space above, the proportion of globulin. A

gradual increase in both fractions of the protein may be noted as the age increases. The averages obtained for the younger infants are in general like those reported by Darrow and Cary[3] although our small series shows less evidence of a high albumin-globulin ratio than they found. The figures obtained in the older infants are distinctly lower than adult levels but higher than those of the younger infants. The average obtained in the group of children from two to fifteen years of age is in accord with the usually accepted normal average for adults.

SERUM PROTEIN LEVELS OF THE CLINIC GROUP

The children studied were divided into the same age groups as the normals. Too few figures on individuals under three months were obtained to be of any significance, and they are not presented here. As disease is known to influence the levels of serum protein, the age groups

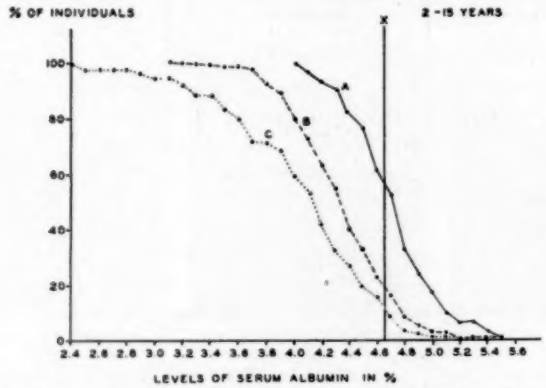

Fig. 2.—Ogive (cumulated downward). Graphic representation of distribution of serum albumin levels in children two to fifteen years of age.

Group A, 33 normal well-nourished children; Group B, 297 clinic patients not ill; Group C, 64 clinic patients ill. Line *X* indicates average normal level.

are subdivided into sick children, nearly all of whom had acute or chronic infections, and children with no significant active disease. Only the figures for the albumin fraction of the serum protein were used in making the charts because this fraction has been shown to be the most important in maintaining fluid relationships and is, as well, the first to be reduced by malnutrition and disease. For convenience in discussing the results, the normal group of children in both age groups will in the future be spoken of as Group A, the clinic children without significant disease as Group B, and the group containing those with acute or chronic infections as Group C.

Figure 2 is a graphic representation of the serum albumin percentages of the children from two to fifteen years of age in the form of ogives. Along the ordinates are plotted the percentages of the group having an

albumin level above that indicated by the figures on the abscissa (cumulated downward). The solid line is the curve for the albumin of thirty-three individuals in Group A, and serves as a basis of comparison with the other groups. The line of dashes represents the albumin figures of the 297 children in Group B, while the dotted line represents those of the sixty-four children of Group C. A perpendicular line is drawn through the curves at the average normal level. There is a distinct tendency for the curves of Groups B and C to run under that of Group A. Whereas 56 per cent of Group A reach or exceed the average normal

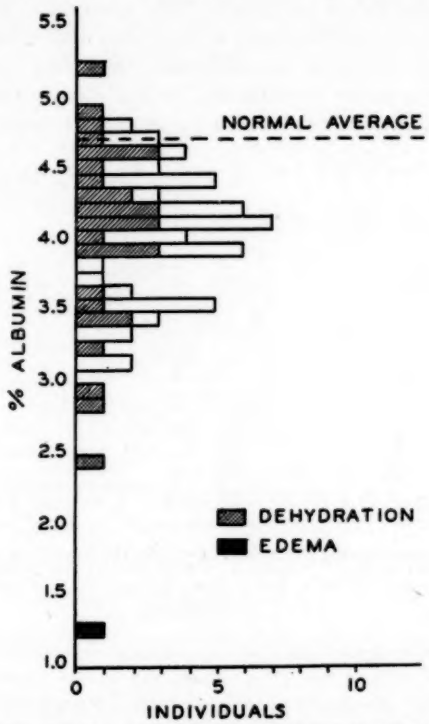

Fig. 3.—Graphic representation of distribution of levels of serum albumin in Group C, aged two to fifteen years, to show incidence of dehydration and edema.

level of albumin, only 20 per cent of Group B and 12 per cent of Group C attain this level. Ten per cent of Group B and 32 per cent of Group C have albumin levels below the lowest figure found in Group A. Many of the children of Group C were dehydrated at the time the sample of blood was taken. This factor would tend to concentrate the serum proteins. Figure 3 is a graphic representation of the albumin levels of the individuals in this group to show the incidence of dehydration.

The results obtained in the age group from three months to two years are presented according to the same plan as those obtained in the older

group. The ogives represent the figures on thirty-four individuals of Group A, fifty-seven of Group B, and forty-one of Group C. At this age the curves of Groups A and B were practically identical. This is at first surprising in view of the results obtained in the older group. On further analysis it was found that the majority of infants who came to our dispensary without a serious illness are those who are being fed under our direction. Thus, although the individuals are unselected as far as this study is concerned, they are probably not a fair sample of the general local clinic population of this age. Either the mothers who feed their infants badly do not seek advice until some acute illness occurs, or the poorly nourished children pick up infection easily. There are many poorly nourished infants in our dispensary, but they are almost all ill. Again, in this age group the albumin levels of Group C run well below both the lower limit of normal and the average of Group A. In order to

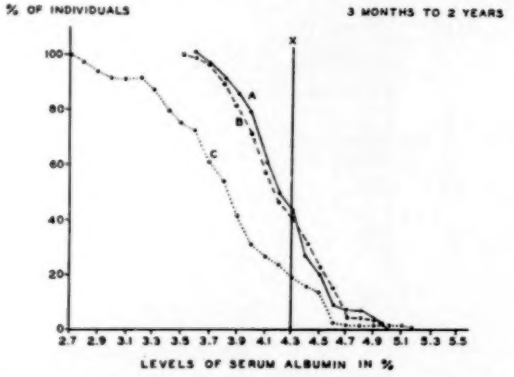

Fig. 4.—Ogive (cumulated downward). Graphic representation of the distribution of serum albumin levels in children from three months to two years of age.
Group A, 34 normal well-nourished children; Group B, 57 clinic patients not ill; Group C, 41 clinic patients ill. Line *X* indicates average normal level.

show the incidence of dehydration in Group C, the results are also shown in Fig. 5. It may be noted that practically every figure which is at or above the normal average was obtained on a dehydrated infant.

A few of the individuals in our clinic group, as may be noted in Figs. 3 and 5, had edema at the time the blood samples were taken. A good many others had concentrations of serum albumin which are at or near the level at which edema often appears. When these children were acutely ill and were given even moderate amounts of subcutaneous saline on admission to the hospital, they often became edematous. In the younger children edema commonly appeared when, because of diarrhea, food and fluid were discontinued by mouth and intravenous and subcutaneous fluids were used instead. One child with celiac disease, whose serum albumin level in spite of marked dehydration was 1.4 per cent on admission, developed a mediastinal effusion when she was

given subcutaneous saline. Another child developed a generalized edema with free fluid in the pleural, pericardial, and peritoneal cavities. We find that we have been obliged to grow more and more conservative about the administration of parenteral fluids, especially saline, and that we must constantly be on the lookout for edema.

We realize that decreased serum protein percentages are not the only factor concerned in the appearance of edema in sick children, even when they have neither cardiac nor renal disease. The intake of salt and water has a great influence on whether or not edema appears at a given degree of hypoproteinemia. Vitamin deficiencies, lack of calcium, and infections all increase the permeability of the blood vessels. We believe, however, that our findings indicate that we are dealing in our

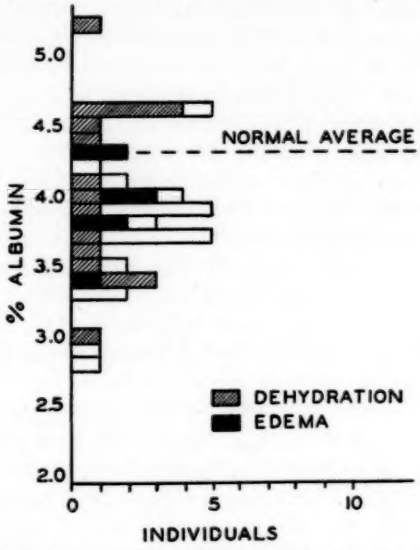

Fig. 5.—Graphic representation of distribution of levels of serum albumin in Group C, aged three months to two years, to show incidence of dehydration and edema.

clinic group with many individuals who already have a hypoproteinemia due to malnutrition and that they develop edema much more easily than normal individuals.

It was hoped that further division of the data according to race, details obtained as to diet, or percentage above or below average normal weight might show more clearly the relation of the diet to the hypoproteinemia. No difference was found between the white and colored children. No marked difference was shown when we divided the children into groups according to whether the dietary history that we could obtain at a single visit sounded reasonably adequate or inadequate. The factor of blood volume which we hope to investigate later may largely explain the lack of conformity between the serum protein levels and the

weights of the children. One response to low protein diets or to depletion of plasma proteins by plasmapheresis in experimental animals is a considerable reduction in plasma volume.[4] This may occur without a significant change in the concentration of plasma proteins, although the total amount of circulating proteins is thereby considerably decreased. If a similar response is made by children on a deficient protein intake, it may explain the finding of normal serum protein levels in some greatly undernourished individuals.

SUMMARY AND CONCLUSIONS

We have presented the results of serum protein determinations in normal children of various age groups. These figures confirm the observations of others that the serum proteins of infants are low and increase gradually to approximately the adult level at two years of age. The general level of serum albumin of our clinic group, even in the absence of acute or chronic illness, is somewhat below that of the normal group. The serum albumin in children with acute or chronic infection rarely reaches the normal average except in the presence of dehydration. A few of the children studied had edema when first seen. Several of the sick and dehydrated children developed edema following the administration of moderate amounts of parenteral saline. This work indicates that a chronic low grade deficiency in serum proteins is common among the poorer children in the community. The diet which is low in total calories and in protein is probably the cause of the deficiency. Such children are predisposed toward the development of edema, especially in the presence of infection.

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SEASONAL VARIATION OF THE BIRTH WEIGHT OF THE NEWBORN

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SINCE Pastor Malling-Hansen (1883) of Copenhagen reported his observations on the periodicity in the gain of weight among children, various individuals, namely, Camerer and Amburg (1912), Bleyer (1917), Porter (1920), Emerson (1927), and others have followed in the same line of research. These workers, though not certain of the cause, came practically to the same conclusion that the growth in weight is accelerated from midsummer to fall and retarded in late winter and spring. This has stimulated the interest of some investigators in finding out whether similar seasonal variations of birth weight occur.

The first study of this kind was made by Adersen (1899). He examined the records of the birth weight and birth length of 2,960 infants born in Stockholm and found that newborn infants were larger in the first (colder) part of the year than those of the succeeding months. Hansen (1913) in his study of birth weight of nearly 6,000 infants of the Nykobing-on-Sealand District of Denmark, observed that infants born in the fall months were heavier than those born in the spring. Abels (1922) studied the birth weights of infants in Vienna. There were 1,166 infants in 1920, and 1,622 in 1921. He found a rise of birth weight from March or April which reached a maximum in August and a minimum in the winter months. He explained this as due to lack of the fat-soluble vitamin A, as during those postwar years people could not afford a sufficient supply of milk, butter, green fruits, or meat in winter. Katz and König (1923) tried to confirm Abels' observations and studied the birth weight of 14,425 infants in Germany; 7,484 of these were born in the years 1910, 1911, 1912, and the remaining 6,941 from the war and postwar years, 1917 to 1920. They combined the figures in the three prewar years to form one group and the four late-war and postwar years into another in order that the effect of change of nutrition in these two periods upon the birth weight might be studied. They found that the birth weight during the war and postwar years was in general below that of the prewar years, and there were small negative monthly fluctuations of the birth weight, but they were unable to say whether these negative fluctuations were due to lack of vitamins in the food. With a view to

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confirming the observations of Abels, Schlossmann (1923) studied the birth weights of 13,805 infants born in the years 1905 to 1922. He was unable to find a diminution in the birth weight in the winter months. Murray (1924) found that infants born in August, 1918 (59 cases), had the greatest birth weight (7.31 pounds), while those born in February of the same year (38 cases) had the lowest (6.78 pounds). There appeared to be a slight falling off in weight in march, which might indicate the unfavorable effect of cold weather during the last three months of pregnancy, but the range was not great, and the question required further study. Dunkin and others (1930) studied the seasonal variation of the birth weights of guinea pigs and found that, in general, albino guinea pigs born in the January-March quarter were below the average in weight and that those born in August and September were above the average; but these observations were not consistent, especially in the case of mixed color families.

Thus far, opinions differ with regard to the seasonal variation in birth weight. Adersen found a greater birth weight in the first half of the year. Hansen, Abels, and Murray found an increase in birth weight in the late summer and early autumn months. Katz, König, and Schlossmann found no definite difference. Dunkin and others found a greater birth weight in some series of guinea pigs during August and September and smaller birth weight in the January-March quarter. The present study is an attempt to ascertain, using some well-known statistical methods of analysis, whether seasonal variation of the birth weight of babies does exist.

The present study consists of two parts: (A) study of data of the Peiping Union Medical College Hospital, and (B) a collective study of available data in the medical literature.

STUDY OF DATA FROM THE PEIPING UNION MEDICAL COLLEGE HOSPITAL

During a period of eight years and four months ending in June, 1930, there were 1,938 obstetric admissions to the Peiping Union Medical College Hospital. The number includes mothers of different nationalities, of various economic status, as well as in various medical conditions. On admission, the patient's name, age, address, occupation, nationality, and nativity were recorded. As a hospital routine, the record of present illness, marital and obstetric histories, and findings from a complete physical examination were required of every patient. The whole labor process and the condition of the infant were also recorded. Illegitimate births were also noted as such.

The temperature in Peiping in the cold months differs significantly from that in the hot months. The cold season begins about the first of November and ends by about the middle of March. The average winter temperature is about 10° F. above zero but the lowest temperature may be as low as 20° F. below zero. The hot season begins

about the middle of June and ends about the middle of September. The average temperature in the summer is about 90° F., but may be as high as 105° F. The months from the middle of September to the end of October and from the middle of March to the middle of June are very temperate. The Peiping weather is quite similar to that of Boston, except that the former is not so humid as that of the latter.

Li (1928), in a study of factors affecting the birth weight of the newborn, found that birth weight undergoes a considerable amount of normal variation, and that it is affected by such factors as nationality, sex, duration of gestation, birth order, multiple pregnancy, size of mother, and health of mother; age of mother under twenty years possibly also exerts an unfavorable effect. In order to avoid the concealed influences of these factors, care is given in the present study to the statistical analysis. Only infants of Chinese parentage are used; all premature births, stillbirths, illegitimate births, and multiple pregnancies are excluded; mothers or infants suffering from tuberculosis, heart disease, eclampsia, syphilis, or pneumonia are not included, though patients suffering from diseases of mild character or short duration such as headache, acute dysentery or diarrhea and surgical conditions are retained. The number thus excluded is 890 cases, leaving a total of 1,148 selected cases of Chinese parentage. This sample is furthermore studied with regard to the age of the mother, nativity of the mother, sex of the infant, its month of birth, order of birth, and birth weight. The nativity of the mother is arbitrarily divided into three groups: the southern, the central, and the northern. Fukien, Kwangtung, Kwangsi, Yunnan, Kweichow, and Hunan provinces belong to the southern group; Szechuan, Hupeh, Kiangsi, Anhuei, Kiangsu, and Chekiang, to the central group; Shantung, Honan, Shensi, Shansi, Kansu, and those provinces north of them, to the northern group. The nativity of the father is not recorded; its omission is probably not important, because the Chinese mother's nativity is usually the same as the father's as she is customarily married to a man of her native province.

Each monthly sample is thus analyzed with respect to possible influence exerted by such factor as mother's age, nativity of mother, sex, and order of birth (Table I); the distribution of these factors throughout the sample is fairly even in all months and they exert no significant influence in the conclusions to be drawn from the data.

The result of this study shows that the monthly means undergo some fluctuation (Table II). The lowest mean occurs in February (2907 ± 44 gm.), while the highest is in July (3185 ± 68 gm.); the difference between these two extreme values is 278 ± 81 gm., which is significant. A closer observation of the whole series of the monthly averages reveals, however, that there seem to exist a decrease in birth weight

TABLE I

PERCENTAGE OF DISTRIBUTION OF 1,148 CHINESE INFANTS BY AGE OF MOTHER, NATIVITY, SEX, BIRTH ORDER, AND MONTH OF BIRTH

		JANUARY		FEBRUARY		MARCH		APRIL		MAY		JUNE		JULY		AUGUST		SEPTEMBER		OCTOBER		NOVEMBER		DECEMBER	
		NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT	NO. OF CASES	PER CENT
Mother's age	19 or 19–	4	4	12	13	5	5	7	7	6	6	4	5	4	5	5	5	9	9	8	8	11	13	8	7
	20 or 20+	95	96	79	87	95	95	93	93	95	94	77	95	81	94	91	95	91	91	92	92	74	87	101	93
	Unknown	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0
	Total	99	100	91	100	100	100	100	100	101	100	81	100	86	100	96	100	100	100	100	100	85	100	109	100
Nativity	Northern	55	56	47	52	52	52	54	54	55	55	44	54	42	49	53	55	56	56	57	57	45	53	54	49
	Central	27	27	26	28	28	28	22	22	25	25	21	26	25	29	25	27	26	26	27	27	25	30	26	24
	Southern	14	14	16	18	17	17	22	22	18	17	14	17	18	21	9	9	16	16	13	13	12	14	27	25
	Unknown	3	3	2	2	3	3	2	2	3	3	2	3	1	1	9	9	2	2	3	3	3	3	2	2
	Total	99	100	91	100	100	100	100	100	101	100	81	100	86	100	96	100	100	100	100	100	85	100	109	100
Infant's sex	Males	44	44	46	51	44	44	55	55	56	55	40	49	42	49	45	47	52	52	42	42	47	55	59	54
	Females	55	56	45	49	56	56	45	45	43	43	40	49	44	51	48	51	47	47	58	58	38	45	50	46
	Unknown	0	0	0	0	0	0	0	0	2	2	1	2	0	0	3	2	1	1	0	0	0	0	0	0
	Total	99	100	91	100	100	100	100	100	101	100	81	100	86	100	96	100	100	100	100	100	85	100	109	100
Birth order	First	42	42	40	44	47	47	54	54	42	41	45	56	29	34	45	47	52	52	46	46	37	44	40	37
	Second	22	22	16	18	24	24	13	13	22	22	16	20	25	29	12	12	15	15	16	16	22	26	32	29
	Third	15	15	16	18	9	9	9	9	12	12	6	7	6	7	13	14	10	10	11	11	10	12	10	9
	Fourth	4	4	11	12	7	7	9	9	8	8	6	7	10	12	7	7	6	6	11	11	7	8	7	6
	Fifth+	16	16	7	7	13	13	15	15	17	17	6	7	16	18	17	18	17	17	16	16	9	10	20	19
	Unknown	0	0	1	1	0	0	0	0	0	0	2	3	0	0	2	2	0	0	0	0	0	0	0	0
	Total	99	100	91	100	100	100	100	100	101	100	81	100	86	100	96	100	100	100	100	100	85	100	109	100

TABLE II

MEAN BIRTH WEIGHT OF CHINESE INFANTS BY MONTH OF BIRTH

MONTH OF BIRTH	NUMBER CASES	BIRTH WEIGHT (GRAMS)
January	99	2,967 ± 37
February	91	2,907 ± 44
March	100	2,965 ± 43
April	100	3,058 ± 39
May	101	3,133 ± 36
June	81	3,029 ± 58
July	86	3,185 ± 68
August	96	3,094 ± 71
September	100	3,045 ± 40
October	100	3,060 ± 48
November	85	3,077 ± 49
December	109	3,053 ± 48
	1,148	Av. 3,037 ± 12

during the winter months and an increase during the summer months. To confirm this a statistical test was made. The cases were distributed or redistributed according to their month of birth into six groups as follows: Group I, births occurring in December, January, and February (the cold months); Group II, births occurring in October, November, and March (the temperate months); Group III, births occurring in April, May, and June (the fairly warm months); Group IV, births occurring in July, August, and September (the hot months); Group V, births occurring from April to September (the warmer half of year), and Group VI, births occurring from October to March (the colder half of the year). These are given in Table III.

The mean birth weight of these six groups indicates the existence of the lowest birth weight in the cold months which increases as the warm weather advances, reaching its maximum during the hot months. The difference between the mean birth weight of Group I and that of Group IV is 165 ± 29 gm. and is very significant, the difference between that of Group V and that of Group VI is 106 ± 18 gm. and is also very significant.

A general glance at Table III reveals certain differences in the way in which the birth weights of each of the six groups are distributed; more cases of light weight occur in the cold months than in the warm months. It remains for one to take the distribution by weight of any group in Table III and compare it with the distribution by weight of any other group by the use of χ^2 test in order to find out whether the distributions of these two groups are significantly different from each other.* The following results are given in Table IV.

The inference drawn in the χ^2 tests is that the distribution of birth weights of infants born in the cold months is significantly different from the distribution of birth weights of infants born in the warm months, as well as that the distribution of birth weights of cases born

*For readers who wish to know detailed procedures in applying the Chi-Square Test, Pearl's *Medical Biometry and Statistics*, ed. 2, Chapter XII, pp. 315-326, may be referred to.

TABLE III

DISTRIBUTION OF CASES ACCORDING TO TIME OF BIRTH AND BIRTH WEIGHT

BIRTH WEIGHT (GM.) / GROUP	CASES OCCURRING IN	1500	1700	1900	2100	2300	2500	2700	2900	3100	3300	3500	3700	3900	4100	4300	4500	4700	4900	5100	5300	...	8100	TOTAL	MEAN BIRTH WEIGHT (GM.)
I	Dec., Jan., Feb.	1	1	3	6	20	34	50	48	58	29	26	14	6	3	0	0	0	0	0	0		0	299	2945 ± 18
II	Oct., Nov., March	1	1	0	8	11	17	48	48	45	51	31	9	9	2	2	2	0	0	0	0		0	285	3042 ± 18
III	April, May, June	0	0	0	2	9	17	37	54	50	54	37	14	4	3	0	1	0	0	0	0		0	282	3088 ± 16
IV	July, Aug., Sept.	0	0	3	8	5	23	37	44	44	52	27	22	9	3	1	1	1	0	1	0		1	282	3110 ± 23
V	April, May, June, July, Aug. Sept.	0	0	3	10	14	40	74	98	94	106	64	36	13	6	1	2	1	0	1	0		1	564	3099 ± 13
VI	Oct., Nov., Dec., Jan., Feb., March	2	2	3	14	31	51	98	96	103	80	57	23	15	5	2	2	0	0	0	0		0	584	2993 ± 13

in temperate months (Group II) is not significantly different from the distribution of the birth weights of cases born in months the temperature of which is not much dissimilar (Group III). This leads to the same conclusion that there exists a real difference in birth weight with respect to season.

TABLE IV

χ^2 TEST FOR SIGNIFICANCE IN DIFFERENCE OF DISTRIBUTION BY WEIGHT OF VARIOUS GROUPS

χ^2 TEST FOR DIFFERENCE IN DISTRIBUTION BY WEIGHT BETWEEN	VALUE FOR χ^2	VALUE FOR P.	INFERENCE
Group I (Dec., Jan., Feb.) and Group IV (July, Aug., Sept.)	26.6866	0.005	Significantly different
Group V (April-Sept.) and Group VI (Oct.-March)	20.9154	0.033	Quite significantly different
Group II (Oct., Nov., March) and Group III (Apr., May, June)	13.5022	0.26	Not significantly different

COLLECTIVE STUDY OF DATA FROM VARIOUS SOURCES

An attempt is made to utilize, in addition to the data given above, samples published by other investigators. Only samples having a minimum of 1,000 infants are chosen. Accordingly, nine sets of data published by six investigators are selected: namely, two sets presented by Abels (1922), two sets by Katz and König (1923), a set by Schlossmann (1923), two sets by Momm (1916), and two sets by Ruge (1916). The first five sets were used by their respective investigators for the study of seasonal variation in birth weight. The last four sets were used by their investigators for study of the effect of poor nutrition upon birth weight, but they can be utilized here for the study of seasonal variation. These give a total of ten sets of data as tabulated in Table V.

Fluctuations in the monthly averages are present in all sets. A reduction in weight during the winter months is observable in most cases. The following plan is adopted to find out whether any uniformity exists in seasonal fluctuation of birth weight. Each set is taken separately; each monthly average is compared with the respective yearly average; if the former is greater than the latter, a plus sign (+) is given; if smaller, a minus sign (–), disregarding the magnitude of such differences. The results, given in Table VI, show a predominance of minus signs during the cold months and of plus signs during the warm months.

Table V

Birth Weights as Reported by Various Investigators

Month of Birth	Li		Abels				Katz and König				Schloss-mann		Momm				Ruge			
	1922-1930		1920		1921		1910-1912		1917-1920		1905-1922		1912		1916		1913		1915-1916	
	No. cases	Mean birth wt. (gm.)	No. cases	Mean* birth wt. (gm.)	No. cases	Mean* birth wt. (gm.)	No. cases	Mean birth wt. (gm.)	No. cases	Mean birth wt. (gm.)	No. cases	Mean birth wt. (gm.)	No. cases	Mean birth wt. (gm.)	No. cases	Mean birth wt. (gm.)	No. cases	Mean birth wt. (gm.)	No. cases	Mean birth wt. (gm.)
Jan.	99	2,967	60	2,938	123	2,998	690	3,075	528	3,101	1,118	3,235	–	3,080	–	3,238	–	3,312	–	3,294
Feb.	91	2,907	64	2,992	143	3,008	581	3,125	580	3,100	1,211	3,232	–	3,111	–	3,166	–	3,228	–	3,351
March	100	2,965	73	3,022	129	2,992	720	3,245	606	3,125	1,281	3,216	–	3,198	–	3,132	–	3,359	–	3,366
April	100	3,058	75	3,098	146	3,015	698	3,200	523	3,076	1,213	3,254	–	3,197	–	3,211	–	3,200	–	3,333
May	101	3,133	94	3,078	155	3,115	703	3,238	602	3,077	1,224	3,205	–	3,159	–	3,047	–	3,266	–	3,155
June	81	3,029	107	3,100	119	3,100	627	3,202	545	3,110	1,249	3,237	–	3,162	–	3,176	–	3,294	–	3,245
July	86	3,185	122	3,145	148	3,090	606	3,238	585	3,112	1,192	3,256	–	3,118	–	3,269	–	3,351	–	3,314
Aug.	96	3,094	123	3,120	109	3,130	543	3.200	606	3,129	1,168	3,222	–	3,237	–	3,217	–	3,259	–	3,293
Sept.	100	3,045	82	3,122	135	3,140	573	3,185	671	3,145	1,127	3,245	–	3,174	–	3,155	–	3,350	–	3,160
Oct.	100	3,060	118	3,120	147	3,145	552	3,168	562	3,129	1,000	3,271	–	3,117	–	**3,162**	–	3,246	–	3,281
Nov.	85	3,077	116	3,068	129	3,100	578	3,153	521	3,061	1,015	3,255	–	3,187	–	3,245	–	3,245	–	3,251
Dec.	109	3,053	132	**3,065**	139	3,030	613	3,142	621	3,070	1,007	3,236	–	3,201	–	3,157	–	3,385	–	3,338
Total	1,148	3,037	1,166	**3,072**	1,622	3,072	7,484	3,181	6,950	3,103	13,805	3,237	1,000	3,162	1,000	3,181	2,000	3,291	1,759	3,282

*Values estimated from curves.

TABLE VI

MONTHLY MEAN BIRTH WEIGHTS ACCORDING TO THEIR RESPECTIVE YEARLY AVERAGES, PLUS SIGN INDICATING EXCESS OF MONTHLY AVERAGE OVER THE YEARLY AVERAGE AND MINUS SIGN INDICATING THE OPPOSITE CONDITION

DATA		JAN.	FEB.	MARCH	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.
Li		−	−	−	+	+	−	+	+	+	+	+	+
Abels	1920	−	−	−	+	+	+	+	+	+	+	−	−
	1921	−	−	−	−	+	+	+	+	+	+	+	−
Katz and König	1910-1912	−	−	+	+	+	+	+	+	+	−	−	−
	1917-1920	−	−	+	−	−	+	+	+	+	+	−	−
Schlossmann		−	−	−	+	−	0	+	−	+	+	+	−
Momm	1912	−	−	+	+	−	0	−	+	+	−	+	+
	1916	+	−	−	+	−	−	+	+	−	−	+	−
Ruge	1913	+	−	+	−	−	+	+	−	+	−	−	+
	1915-16	+	+	+	+	−	−	+	+	−	−	−	+
Total	(+)	+3	+1	+5	+7	+4	+5	+9	+8	+8	+5	+5	+4
	(−)	−7	−9	−5	−3	−6	−3	−1	−2	−2	−5	−5	−6
	Sum	−4	−8	0	+4	−2	+2	+8	+6	+6	0	0	−2

Now, the question is this: Can the predominance of minus signs during the cold months or that of plus signs during the warm months be explained by the matter of chance variation? In order to answer this question, the months of birth are grouped into six groups as previously; the plus signs and minus signs belonging to each group are summed; two groups are taken at a time and subjected to the χ^2 test; the results are given in Table VII.

TABLE VII

TEST FOR SIGNIFICANCE IN DIFFERENCE IN DISTRIBUTION OF THE PLUS AND MINUS SIGNS AMONG VARIOUS GROUPS

GROUPS	+	−	TOTAL	
V. April, May, June, July, Aug, Sept.	42	18	60	$\chi^2 = 3.463$ $P = 0.0004$
VI. Oct., Nov., Dec., Jan., Feb., March	23	37	60	Inference: Difference is very significant
Total	65	55	120	
I. Dec., Jan., Feb.	8	22	30	$\chi^2 = 5.983$
IV. July, Aug., Sept.	25	5	30	$P = 0.0000$
Total	33	27	60	Inference: Difference is very significant
II. Oct., Nov., March	15	15	30	$\chi^2 = 0.578$
III. April, May, June	17	13	30	$P = 0.95$
Total	32	28	60	Inference: No difference

These results indicate that the prevalence of lower monthly averages than the yearly average in the cold months and the opposite condition in the warm months cannot be explained by the matter of chance; and this supports the findings of smaller birth weight in the cold months and a greater birth weight in the warm months.

DISCUSSION

The study of seasonal variation of birth weight is not a new one. The present findings are similar to those of Hansen, Abels, and Murray. The reason for lack of uniformity in the results obtained by all of the previous workers is probably due to nonappliance of statistical procedures; the normal variation of birth weight itself is large; and results are thus hard to be drawn without statistical considerations. Besides, there are so many other factors which may exert concealed influences in the averages and which should be carefully ruled out before inference can be drawn.

S. W. Li (1930) studied the birth weight of practically the same sample of Chinese babies born in the Peiping Union Medical College Hospital and found that male babies weighed more than the female, the average weights being 3,124 gm. and 2,980 gm., respectively, with a difference of 144 gm. According to Table III, the difference between the mean birth weight of babies born in the warm months (Group IV) and that in the cold months (Group I) is 165 ± 29 gm. and is probably somewhat greater than the difference due to sex.

It is interesting to note that seasonal variations of birth weight are in agreement with those of the growth of the school children. It would also be interesting to make further study of the birth weights in places where seasonal changes in temperature are negligible. It is possible that, in these places, the seasonal variation of birth weight does not exist; and if it is so, it may be one of the causes for the discrepancy which previous investigators had brought out.

SUMMARY

1. A statistical study of seasonal variation of birth weight has been made, using data collected from the Peiping Union Medical College Hospital and published statistics.

2. The present study shows the existence of a reduction in birth weight in the winter and early spring months and an increase in the late summer and early autumn months.

I wish to thank Dr. I. C. Yuan for many valuable suggestions in this study.

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THE PROPHYLAXIS OF ALLERGIC DISEASE

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ROWE[1] has made the statement that allergy, next to infection, is probably the most important single etiologic agent in human symptomatology. If this statement is correct, the importance of prophylactic measures in allergic disease is easily understood. Since the fundamental constitutional abnormality which makes an individual susceptible to allergic disease is unknown, a completely rational system of prophylaxis cannot be advanced. Nevertheless, certain facts are known, and theories have been brought forward which deserve consideration in the study of this problem. It is rather remarkable that but one paper, that of Peshkin,[2] has been published on this subject. The reason is perhaps that the problems in allergy have been and still are mainly those of finding the allergens responsible for disease in individual cases, and the treatment of disease from that standpoint. The purpose of this communication is to emphasize again some of the facts brought out by Peshkin and to add to these observations made since his paper was published.

Based upon our present knowledge, probably the first step in prophylaxis is the avoidance of marriage between allergic individuals. Of the few fundamental facts known concerning allergic disease, none is more firmly established than the fact of the inheritance of the allergic constitution. Vaughan[3] has pointed out that when the inheritance is unilateral, about 30 per cent of the offspring develop allergic symptoms during the first ten years of life. When the inheritance is bilateral, about 90 per cent of the children develop allergic disease during the first decade. Naturally this does not mean that in every case the allergic disease will be of a disabling nature; the symptoms may be only a transient eczema or croup in infancy or a mild case of pollenosis in one of the children. On the other hand, no practicing allergist can fail to be impressed by the tragedy of a situation in which one of the parents may be disabled by asthma, for example, and all of the offspring afflicted with severe forms of eczema, urticaria, or asthma. The suffering involved and the economic and psychic strain placed upon the family may be very real and serious. Before a marriage is undertaken between allergic individuals it is only fair, if children are desired, for the well-informed physician to explain the facts to one or both of the contracting parties so that they may decide whether or not the gamble is worth while.

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The next most important step in the prophylaxis of allergic disease is the careful observance of the diet of the pregnant mother in a family in which there are allergic diseases in the ascendants of the expected child. The basis of this is largely conjecture from animal experimentation, mainly the work of Ratner and his associates[4] on the active and passive sensitization of guinea pigs in utero. Reasoning from these experiments, pica, the unnatural craving of the pregnant woman for specific articles of diet which she may eat in large amounts, is to be avoided because of the possibility that the offspring may be sensitized to that particular food. Ratner[5] has reported cases where this appeared to be a factor. The pregnant mother should doubtless, with the possible exception of egg, have a varied diet without emphasis upon any one particular article of food.

It is well known that the manifestations of allergic disease in infancy are principally those of food allergy. In the food allergy of infancy, egg plays a particularly significant rôle. According to Hill and Sulzberger,[6] 85 per cent of all infants who react with positive skin tests do so to egg. This is true regardless of the fact that the infants have never ingested egg and may have fed only on the bottle and thus, also, have not had an opportunity to become sensitized to egg protein as a result of the passing of that substance through the mother's breast milk. Sensitization to egg must, therefore, occur in utero, and the mechanism is probably similar to the production of intrauterine sensitivity in guinea pigs in the experiments of Ratner[4] mentioned above. Hill and Sulzberger[6] state that since egg albumen has the lowest coefficient of digestibility of any protein and is the one most easily absorbed into the blood in its natural state, the human fetus, therefore, has ample opportunity to become sensitized to egg in utero. It is well known clinically that when marked sensitivity to one antigen occurs, upon the exhibition of that antigen the protective mechanism is often broken down so that sensitization to other antigens may follow rapidly. Since this is true, it is theoretically possible that by avoiding sensitization of the fetus to egg, perhaps subsequent sensitization to other substances may be diminished, delayed, or aborted altogether. The obvious step, therefore, is for the prospective mother of the potentially allergic child to avoid egg in her diet. Since food sensitivity has a tendency to be inherited in a specific manner, i.e., children whose parents are sensitive to a particular food tend themselves to be sensitive to that food, the indication is to avoid during pregnancy those foods which have previously been responsible for allergic disease in the family. The degree to which egg and other foods should be avoided cannot be stated definitely in the present state of our knowledge, so probably it is better to err on the side of safety and omit the potentially dangerous foods altogether. Because of the clinical fact that antigens may be transmitted through the breast milk

to cause allergic disease in the nursing infant, what holds true for the diet of the mother during pregnancy should probably hold true while she is nursing her child.

Calcium has long been thought to play an important part in the mechanism of allergic reactions, although its use as a therapeutic agent in any form of allergic disease is almost uniformly disappointing. It is unnecessary to go into detail concerning calcium because for reasons other than those associated with allergy the fetus requires liberal supplies of calcium. This should be taken by the mother in the form of milk or, if this is contraindicated, in the form of one of the numerous compounds of calcium now available as a substitute for milk calcium. Adequate amounts of a reliable vitamin D preparation or the utilization of sunlight or ultraviolet radition should be employed to insure utilization of the calcium so ingested. If this is done, at least the theoretical needs of the infant for calcium as a prophylactic agent against allergic disease will be well provided.

The next steps in the prophylaxis of allergic disease lie in the hands of the pediatrician, having been passed to him, as has been outlined above, from the general medical adviser of the parents of the potentially allergic child through the medium of the obstetrician. In the history of the development of the modern knowledge of allergy, pediatricians have played an important part. The term allergy was invented by the Austrian pediatrician, von Pirquet; and Schloss, formerly professor of pediatrics at Cornell, gave tremendous impetus to the clinical study of allergy when he made the first skin tests for foods in 1912. The more recent contributions of Hill have carried on the interest of the pediatrician in this field.

The pediatrician should consider both the environment and food of the potentially allergic child. Too little attention has been paid to the factor of environment. The clothing of the potentially allergic child should consist almost exclusively of cotton goods. Theoretically, wool, because it is an epidermoid, should be avoided, but practically it seldom causes trouble, even in infants with the worst allergic antecedents, and may be considered fairly safe to use, though the knowledge of its potential danger should be kept in mind. The foregoing remarks apply only to wool cloth and not to wool in the form of fur, as a sheepskin coat or blanket. Pure linen may be used but is not popular on account of the expense of the better qualities. Silk should never be used in the clothing, bedding, or hangings of the room of a potentially allergic child as the experience of recent years has shown that it is a frequent and dangerous antigen. It is too often forgotten that silk is of animal epidermoid origin and like most epidermoids has a great sensitization potentiality. Feather pillows and hair mattresses are to be avoided in the prophylaxis of allergic disease. Too many cases of sensitivity to

these substances develop in later life to risk their presence when adequate substitutes as cotton or kapok or synthetic nonallergic materials are available.

Following the same line of reasoning fur-bearing or feather-bearing animal pets and furred toys are to be avoided in the environment of potentially allergic children. Dust sensitivity in childhood has been quite common in our experience, and while there is no way of escaping dust, dust-catching and dust-hiding furniture should be avoided, at least in the rooms of potentially allergic children. Toilet preparations containing orris root are not to be used because of the frequency with which sensitization occurs to that substance. Probably the safest preparations are those manufactured by several companies particularly for the use of allergic individuals. The use of dusting powders or insect exterminators containing pyrethrum is also bad practice because sensitivity to pyrethrum, a fairly close relative of the ragweed, is of frequent occurrence.

The pediatrician first comes into contact with food allergy ordinarily when the infant develops colic or eczema or both. While there can be no doubt that the symptom-complex of irritability, apparent peristaltic cramps, distention of the abdomen and eructations of gas, or the passage of excessive flatus, commonly called colic, can be due to causes other than allergy, careful observation will indicate that food allergy is responsible in many cases and deserves particular consideration in the potentially allergic child. The principal way in which colic is treated is by a change in the infant's diet which involves a modification of the ingested proteins. It is the opinion of the authors that food allergy is to a certain extent a natural physiologic phenomenon. This is suggested by the fact that as new foods are added to the infant's diet, an eosinophilia occurs which disappears as the infant becomes accustomed to the new food.[7] It has been shown by Peshkin and Rost[8] that 10 per cent of normal children between the ages of two and fifteen years show positive or doubtful skin reactions which decrease as age advances, indicating, according to them, progressive desensitization. It is the inability of the potentially allergic child to make the adjustment to foods and other antigens which causes the appearance of symptoms which rise to a clinical level with the development of obvious allergic disease. In the potentially allergic infant, colic and eczema, even in their milder forms, are not to be lightly regarded because the child will "outgrow" the symptoms, as the physician commonly states. The potentially allergic child has a very real chance of developing intractable eczema or asthma. For this reason food modifications are to be employed early and with necessary frequency; the pediatrician should not hesitate to make radical changes to alleviate even mild symptoms of allergy in the potentially allergic infant.

According to the same line of reasoning, as with the avoidance of epidermoids, foods possessing a high degree of sensitizing power, such

as eggs, should be added very carefully to the diet and in small amounts. In the definitely allergic infant we do not as a rule introduce egg in the diet until the child is a year old, and then only with extreme care. It is our practice to accustom the potentially allergic infant gradually to egg by starting with minute amounts, as ¼ teaspoon of a raw egg yolk mixed with the total day's formula of the three-month-old infant. If the child tolerates this small amount, the quantity of egg yolk is increased weekly until the child gets a whole raw yolk in his formula daily. Then egg white is added in a similar manner. The egg yolk contains the same proteins as the white, but in a much more diluted form, and by this procedure too much strain on the infant's protective mechanism may perhaps be avoided. The mother is warned to discontinue egg immediately if the child develops colic, a skin rash, or other untoward symptoms, as vomiting or diarrhea. Several months are allowed to elapse before egg is again added to the diet.

The addition of vitamin C to the infant's diet, particularly in bottle-fed babies, is of paramount importance, the common practice being to supply this by means of orange or tomato juice. Allergy to these substances is more frequently manifested by belching or undue spitting up than by colic or a skin rash. If this is the case, the pediatrician may substitute pineapple or turnip juice in equivalent amounts to supply the necessary vitamin C. Turnip juice, while little used for infant feeding in this country, is employed to a considerable extent in Europe because of the greater expense of the other juices. In extreme cases we have resorted to the substitution of 20 mg. of cebione (ascorbic acid, Merck) daily to supply the necessary vitamin C instead of fruit or vegetable juice, apparently with good results. The cebione should not be added to the formula but should be given separately to avoid its destruction by oxidation, which occurs rapidly in water and more rapidly in milk, especially if the reaction is not acid. Cebione is also destroyed by boiling.

Allergy to cod liver oil is most unusual and has not occurred in our practice. Cases have been reported by Balyeat and Bowen;[9] when this occurs vitamin A may be supplied by carotene in oil and vitamin D by viosterol. These substances we employ routinely in children who give positive skin tests to fish, although we have never noticed ill effects from cod liver oil in infants giving even extreme reactions to the cod fish protein test. The work originated by Hansen[10] showed there was a deficiency of unsaturated fatty acids in the blood of allergic eczematous infants. If this is found generally true of allergic infants, it suggests the addition of oils high in unsaturated fatty acids, as corn oil or linseed oil, to the diet of the potentially allergic infant. The application of this in such cases, however, awaits further investigation.

The diet of the potentially allergic child should be varied in order to avoid undue emphasis upon any one food. Cereals other than wheat

should be used when possible because wheat will, in most cases, unavoidably form the bulk of the cereal taken in later life. As substitutes for wheat, rye, rice, oatmeal, corn meal and barley are available, and, if desired, sago, tapioca, and arrowroot. Buckwheat should be used sparingly as it has a high sensitization potentiality. The Irish and the sweet potato may also be classed as cereals. It is preferable to give the potentially allergic infant a single pure cereal instead of the proprietary mixtures of several cereals which are now on the market and are proving highly satisfactory in the feeding of the majority of nonallergic infants. By using single pure cereals instead of mixtures, the child's cereal diet may be easily changed from one to another, and the possibility of simultaneous multiple sensitization is avoided. In the same way it is preferable to start the infant on single vegetables rather than on a mixture such as is found in the usual vegetable soup. Later, when it has been determined which vegetables, cereals, and meats agree with the infant, the soup may be made from those ingredients. Fish must be added with extreme care. We add minute amounts of canned tuna fish or salmon at about the ninth month once or twice a week, and stop these if allergic symptoms appear. We do not care to have our older children indulge in nuts, especially cocoanut and Brazil nuts, and also strawberries, and shellfish. Potentially allergic children should be careful to avoid overindulgence as the fresh vegetables and fruits appear each season because of the common occurrence of urticaria following their ingestion.

As the potentially allergic child develops, considerable attention should be paid to what the parents or even the physician may regard as food whims. That is to say, for no apparently valid reason the child may express a hearty dislike for some particular food which he is compelled to eat because "it is good for him." In the potentially allergic child these food dislikes often represent instinctive defensive reactions to foods which are actually or potentially harmful to the child. In practice this is borne out time after time when an allergic child reacts to those foods which a carefully taken history reveals he has always disliked. On the contrary, it must not be forgotten that a child may be very fond of some particular food to which he is highly sensitive. The important thing to remember is that there are few foods for which an adequate substitute cannot be found, and in the case of allergic or potentially allergic children who dislike particular foods, it is better to give the child the benefit of the doubt. Most of the relatively few problem children met with in our allergic practice have developed feeding problems because of the mistaken efforts of parents or physicians who were unwilling to do this or were uninformed upon this point.

The prophylaxis of allergic disease is important with respect to the procedures which pediatricians should take to protect the child from the usual contagious diseases. The prophylaxis of diphtheria by the use of the usual toxin-antitoxin mixtures, which unavoidably contain minute

amounts of horse serum protein, is to be particularly avoided and has never been practiced by us. Tuft[11] stated that about 28 per cent of children are sensitized to horse serum by this procedure, and that this is much more likely to occur in allergic children or children of allergic families. Perhaps this is one reason why allergic disease appears to be much more common now than it did when our parents were children. We formerly used, on the advice of Dr. I. Harrison Tumpeer, a special diphtheria toxin-antitoxin derived from sheep serum, sensitization to sheep serum being of comparatively little importance. Since toxoid for immunization against diphtheria was introduced, we have used only that product because as far as is known there is no danger of protein sensitization from that source.

Peshkin[2] pointed out that in a series of 100 cases of asthma in children ranging in age from six months to fourteen years, the attacks were initiated in 15 per cent of cases by pertussis, in 14 per cent by pneumonia, in 4 per cent by measles, and in 2 per cent by scarlet fever. Diphtheria and varicella were not observed to initiate the onset of asthma in a single case, which seems peculiar in view of the extensive use of diphtheria antiserum derived from horses. While the value of our latest prophylactic agents against whooping cough, namely the Sauer vaccine and the Krueger unaltered bacterial protein solution, is yet to be proved, personal experience since these were introduced leads us to believe that they have considerable merit and at least do no harm. We use the Sauer vaccine as a prophylactic at any age in the case of allergic children but with our potentially allergic children we have employed it only in infancy. Severe reactions to the vaccine are common in children over a year of age and are best avoided by discovering the child's tolerance by means of small initial doses.

As yet we have no adequate method for the prophylaxis of the various forms of pneumonia, but in allergic children who have had repeated attacks we have had occasional brilliant success by the employment of measures directed against the underlying allergy, as the elimination of, or treatment with, substances to which the child reacted and by the use of vaccines.

Measles is easily prevented or modified by the intramuscular injection of whole citrated blood, preferably from an older member of the family who has had measles. When we employ blood for such purposes, as well as transfusions for any purpose, we prefer to use the parent on whose side there is no history of allergy in order to avoid the possible passive sensitization of the recipient and the breaking down of his protective mechanism.

We do not attempt to immunize our infants actively against scarlet fever by means of the Dick treatments, as local experience has been unsatisfactory with this procedure. We prefer to protect our exposed

children, potentially allergic and otherwise, passively by the intramuscular injection of human convalescent scarlet fever serum, using pooled serum when available.

A simple procedure for active immunization against tetanus is highly to be desired. Perhaps it will not be long before a practical toxoid for this purpose will be available. The work of Bergy[12] and of Sneath and Kerslake[13] indicates that considerable progress has been made in that direction. The reason that this procedure is desirable is that there are at times, following an injury, few more perplexing problems than whether or not tetanus antitoxin should be administered, because the resulting serum reaction may be much more serious and cause much more disability than the original injury. Furthermore, many individuals suffering from severe allergic disease trace the onset of their condition to the injection of such serum. Their allergic balance has been so disturbed by the injection that they develop other allergic diseases following the original serum reaction. However, because of the serious results which might follow the development of tetanus, the physician has no choice but to administer antitoxin in case of reasonable doubt. For the past two years for this purpose we have used a preparation made from bovine instead of horse serum. Reactions occur, but they have not been nearly as frequent or severe as those following the usual antitoxin made from horse serum. If the bovine serum is used, there is a theoretical possibility of sensitizing a potentially allergic individual to lactalbumin, which is considered to be the same substance as serum albumin. Whether or not this will happen must be borne out by future experience.

As the potentially allergic child grows older, the allergy-minded pediatrician will watch carefully for the development of symptoms of pollenosis (rose or hay fever). If a child has a "summer cold" every year at the same time, the diagnosis is almost certain. It is not our practice, however, to treat such children until the diagnosis is obvious to the parents for the reason that without this their cooperation is difficult or impossible to secure. It is our practice with allergic children, regardless of the presenting complaint as eczema, asthma, or urticaria, to test routinely with ragweed and timothy pollen, in addition to the allergens usually indicated. We have observed the frequent occurrence of positive reactions to pollens in children who have never had pollenosis. In many of these children pollenosis has subsequently developed; and now because of this, if we give these children periodic injections of any kind for the presenting allergic complaint as, for example, the injection of house dust extract or vaccine for asthma, we also add the pollens to which the child reacts. We believe, although as yet we have no proof, that this may prevent the future development of pollenosis. That this is probably true is indicated by the recent work of Biederman.[14] He found that of patients who react positively to pollens of one season and have symptoms, but who also have a skin sensitivity to pollens of an additional season,

approximately 5.5 per cent will develop symptoms to the latter the following year, and that patients hyposensitized against all important pollens to which they are skin sensitive remain symptom-free from the pollens to which there are added skin reactions.

The importance of repeated head colds as an allergic manifestation has been pointed out particularly by Cohen and Rudolph.[15] The differential diagnosis between allergic coryza and infectious coryza is usually not difficult, particularly in children. For details of this, reference is made to their publication. If allergic coryza is successfully diagnosed and treated, its most common sequella, asthma, may perhaps be prevented. In this connection the question of the importance of tonsils and adenoids with respect to asthma and pollenosis is often asked. Bullen[16] has tersely summed up the situation in three sentences: Tonsillectomy does not aid in improving the results of treatment of nasal or pulmonary manifestations of allergy. Rare exceptions may occur. Nasal or pulmonary manifestations of allergy are as likely to occur in an individual whose tonsils have been removed as in one who retains his tonsils. For these reasons, in our pediatric practice, we do not differentiate between our nonallergic, potentially allergic, or allergic children with regard to the indications for tonsillectomy and adenoidectomy.

In early childhood the pediatrician caring for the potentially allergic child should bear in mind the possibility that many diseases of obscure origin may possibly have an allergic basis. By detecting their origin early the possibility is presented of clearing up these diseases and preventing their development into more malignant forms of allergic disease. Childhood illnesses which may at times be on an allergic basis are anorexia nervosa, cyclic vomiting (perhaps a childhood form of migraine in which the abdominal instead of the cranial symptoms predominate), pylorospasm, chronic constipation or diarrhea, abdominal pain of obscure origin, enuresis, epilepsy, and perhaps many others. Because of the fundamental pathologic physiology of allergic disease, spasm of smooth muscle and edema, or both, and the number of tissues in which it is possible for these to occur, it is not surprising that almost any disease may be simulated by allergy.

In the field of sports the potentially allergic child deserves some consideration. If he rides or raises animals as a hobby, evidence of sensitization to the specific epidermoids involved must be watched for, or these activities should be avoided altogether. The potentially allergic child who easily suffers from respiratory infections should not be encouraged to swim and dive in cold water, and skating should be indulged in very cautiously. Such a child should not mistakenly be subjected to "hardening processes" as cold showers and sleeping in cold rooms. Without competent medical supervision such treatment is more likely to kill than to cure.

Finally the questions arise as to the climate in which the potentially allergic individual is to live and the occupation he is to follow, though the control of these factors is not always practical or expedient. If the family tendency to allergy is expressed by respiratory tract disorders, a warm, dry climate is to be preferred. On the details of this subject there is very little available in allergic literature. Contributions, as the forthcoming publication of Baldwin,[17] are greatly to be encouraged. In the choice of a profession the parents of the potentially allergic child and his physician should consider the possible antigens to which he may be exposed and the effect of disabling allergic disease if these occupations are undertaken. A youth highly sensitive to silk should not be encouraged to enter the women's dress goods business; a boy with pollenosis should not become a professional golfer; a boy sensitive to flour dust should not become a baker; or one sensitive to feathers, a raiser of poultry. All these incidents have happened in our practice.

It is realized that the considerations presented in the foregoing discussion are in many instances highly theoretical, controversial, and often impractical. Nevertheless, we believe that the discussion offers a point of departure for the consideration of the life program of the potentially allergic individual. The specialty of allergy is old and accomplished enough so that no apologies need be made for it. On the other hand, it is so immature and its shortcomings so obvious that specific promises cannot be made for the future. We may hope by the application of what knowledge we have concerning the origin of allergic diseases, their natural history, and the healing forces of Nature to make an honest attempt to make life easier for those whose constitutions might well subject them to considerable distress from annoying chronic diseases.

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STUDIES ON THE MODE OF ACTION AND THE METABOLISM OF VITAMIN D

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UNTIL the present time our knowledge of the mode of action of vitamin D has been extraordinarily meager and may be summed up almost entirely in the observation that vitamin D increases the diminished inorganic phosphate content of the blood in rickets and brings back to normal the diminished calcium content in spasmophilia. As soon as one raises the question how vitamin D brings about the regulation of inorganic phosphates and calcium in the blood, one enters a vast field of speculation.

One of the hypotheses is the assumption that irradiated ergosterol stimulates an endocrine gland. The work of Erdheim,[1] Pappenheimer and Minor,[2] Ritter[3] and others seemed to indicate the importance of the parathyroid glands in infantile rickets, while the recent publications of Nitschke[4] emphasized the connection between the lymphoid tissues (spleen, lymph nodes, and thymus) and the thyroid gland in regulating the phosphorus and calcium content of the blood. The results of all these studies are, however, far from conclusive, for the simple reason that it has never been possible to isolate any substances other than irradiated sterols that would regulate the inorganic phosphorus content of the blood or would cure rickets. The close relationship between calcium and phosphate metabolism, as well as the discovery by Collip[5] of a hormone regulating calcium metabolism, has, however, made it at least plausible to assume the existence of a hormone regulating phosphorus metabolism.

Two years ago I[6] found that thyroxine elevates the inorganic phosphate content of the blood of healthy infants, an observation that has recently been confirmed by Rietschel.[7] I pointed out, however, that this does not mean that thyroxine can be regarded as the phosphate-increasing substance when rickets is cured by vitamin D. As a matter of fact, I found later[8] that thyroxine does not alter the excretion of phosphorus and calcium through the feces and urine in the same manner as is observed when vitamin D is given.

That is to say, up to the present time we do not know any substance that can be considered a phosphate hormone produced by an endocrine gland through the stimulating effect of irradiated ergosterol.

The importance of this question in understanding the physiologic action of vitamin D and the pathogenesis of rickets, as well, induced me to approach the problem in another way.

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Warkany[9] found that the administration of one large dose of vigantol to rabbits led to a definite increase in the inorganic phosphate content of the blood, an increase which, as I will show later, is not accompanied by a similar effect on the calcium content.

My assumption, in undertaking the studies presented, was that if vitamin D brought about this rise in inorganic phosphate in rabbits' blood by stimulating the production of a phosphate hormone, the chances were that this hypothetical substance might be found in their blood if it was taken at the peak of the vitamin D hyperphosphatemia.

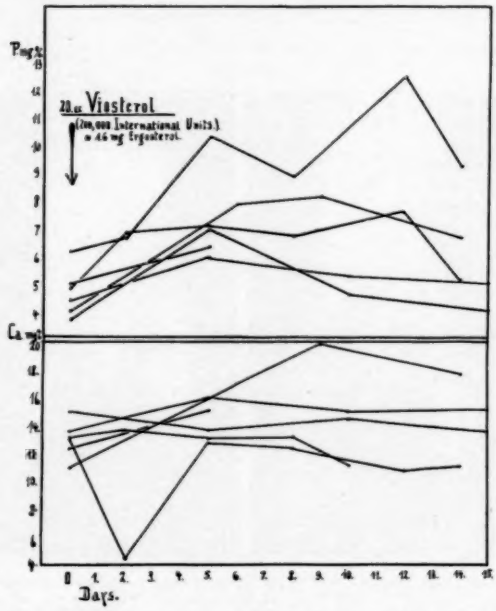

Chart 1.—Curves showing response of inorganic phosphate and calcium in the blood of rabbits after a single dose of 20 c.c. of viosterol in oil (200,000 international units of vitamin D, or about 1.6 mg. of irradiated ergosterol).

The assumption that there was such a substance would be justified if it was found that the blood serum of these rabbits cured rachitic rats by increasing the diminished blood phosphates, *provided that it could be proved that the curative substance did not represent irradiated ergosterol itself.*

Warkany in his experiments used 100 mg. of irradiated ergosterol given as vigantol. The antirachitic preparations of today, however, are quite different from the vigantol of that time (1929). They contain less ergosterol and certainly fewer toxic by-products. It was necessary, therefore, to repeat Warkany's experiments, using modern ergosterol preparations. These results are now reported.

To rabbits weighing from 3,000 to 4,000 gm. 20 c.c. of viosterol in oil was administered by stomach tube. This is a large dose, representing 200,000 international units of vitamin D; however, it is equivalent to approximately 1.6 mg. of irradiated ergosterol—in other words, a dose less than one-fiftieth of that used by Warkany. The blood of the rabbits was obtained from the femoral vein, and duplicate phosphorus and calcium determinations were made by the titrimetric method of Samson[10] using 1 c.c. of serum for each determination.

Chart 1 shows that, from five to ten days after viosterol was given, the inorganic phosphate content of the blood increased and remained elevated for from the tenth to the fourteenth day, while no regular and definite response was found in the calcium content of the blood.

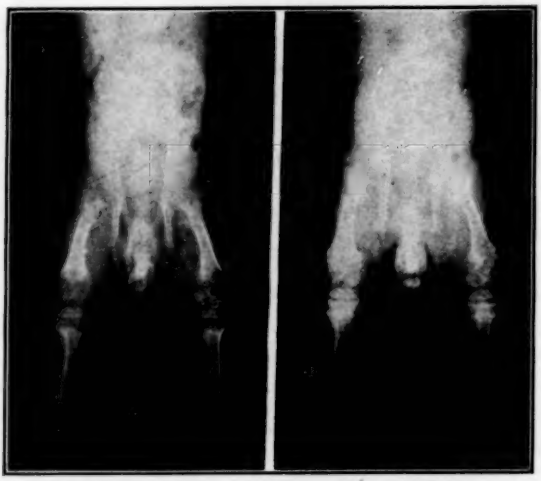

Fig. 1.—Roentgenograms of Rat 5397 (see Table I) before (left) and after ten daily (right) intramuscular injections of 0.6 c.c. of rabbit serum. Rabbit 446, from which the serum was taken, had been given, six days previously, 20 c.c. of viosterol (200,000 international units of vitamin D, or about 1.6 mg. of irradiated ergosterol).

If it were true that this hyperphosphatemic response was due to the production of a phosphate hormone, the shape of the curves in Chart 1 would indicate that its greatest concentration in the blood was on the fifth to the tenth day after the administration of vitamin D, because the greatest stimulation of the phosphate metabolism occurred at that time.

Consequently, I took the blood of the rabbits on the fifth to tenth day after the viosterol had been given and injected daily, for ten consecutive days, 0.6 c.c. of the serum intramuscularly in rats which had been for three weeks on a rickets-producing diet (Steenbock No. 2965).

The results of these five experiments, recorded in Table I, show that the rabbit serum possessed high antirachitic potency in each of the

thirteen rats used. The roentgenographic findings in all the rats were without exception the same as those shown in Fig. 1 (Rat 5397).

TABLE I

HEALING OF RACHITIC RATS BY INTRAMUSCULAR INJECTION OF 0.6 C.C. OF SERUM OBTAINED FROM RABBITS GIVEN 200,000 INTERNATIONAL UNITS OF VITAMIN D BY MOUTH (20 C.C. OF VIOSTEROL) FIVE TO TEN DAYS PREVIOUSLY

RAT NO.	TREATMENT	X-RAY HEALING AFTER		SERUM			
				OF RABBITS		OF RATS*	
		EIGHT DAYS	TEN DAYS	P MG. %	Ca MG. %	P MG. %	Ca MG. %
5392 5393 5396	Rabbit 445 on 11/3/34 received 20 c.c. of viosterol. On 11/13/34 its blood was taken and 0.6 c.c. of this serum injected daily in the rats.	++ ++ ++	+++ +++ +++	6.37	12.4	5.15	18.6
5397 5399 5401	Rabbit 446 on 10/31/34 received 20 c.c. of viosterol. On 11/5/34 its blood was taken and 0.6 c.c. of this serum injected daily in the rats.	++ ++ ++	+++ +++ +++	10.3	14.6	5.5	14.4
5452 5453 5459	Rabbits 447 and 448 on 12/22/34 each received 20 c.c. of viosterol. On 12/27/34 their blood was taken and 0.6 c.c. of this mixed serum injected daily in the rats.	++ ++ +++	++++ +++ ++++	12.2	14.0	5.43	13.6
5533 5534	Rabbits 458 and 457 on 2/19/35 each received 20 c.c. of viosterol. On 2/25/35 their blood was taken and 0.6 c.c. of this mixed serum injected daily in the rats.	++ ++	++++ +++	5.1	15.0	3.99	--†
5636 5637	Rabbits 468 and 469 on 4/15/35 each received 20 c.c. of viosterol. On 4/20/35 their blood was taken and 0.6 c.c. of this mixed serum injected daily in the rats.	++ ++	+++ ++++	7.0	15.0	4.94	11.2
	Averages					5.0	16.9

*Throughout these studies the rats were killed ten days after treatment had been started so that their blood was obtained for determination of phosphorus and calcium on the same day on which the last roentgenograms were taken. Phosphorus and calcium contents of blood serum are given in milligrams per hundred cubic centimeters.

†Serum for determination was lost.

Several control experiments must be reported here before any further discussion can take place.

It was first necessary to prove that rats kept under the same conditions as were the experimental animals did not show any healing without treatment; furthermore, that the serum of rabbits which had never received viosterol did not cure the rachitic condition; and, finally, that the curative effect of the serum of those rabbits which had received the large vitamin dose was not due to the increased phosphate content—a question that could be decided by injecting aqueous solution of Na_2HPO_4 in the same concentration as was present in the serum.

The results from the group of control experiments were entirely negative and are presented in Table II.

TABLE II

CONTROL EXPERIMENTS

RAT NO.	TREATMENT	X-RAY HEALING AFTER		SERUM OF RATS*	
		EIGHT DAYS	TEN DAYS	P MG. %	Ca MG. %
5388	None	0	0	3.77	14.0
5394		0	0		
5395		0	0		
5398	None	0	0	5.71	13.0
5400		0	0		
5402		0	0		
5380	Received daily intramuscular injections of	0	0	4.72	13.0
5382	0.6 c.c. of serum from healthy Rabbit	0	0		
5383	450 which did not receive viosterol.	0	0		
5385	Received daily intramuscular injections of	0	0	4.72	11.8
5389	0.6 c.c. of serum from healthy Rabbit	0	0		
5391	448 which had not received viosterol.	0	0		
5448	Received daily intramuscular injections of	0	0	5.15	10.4
5455	0.6 c.c. of serum from healthy Rabbit 449 which did not receive viosterol.	0	0		
5649	Received daily intramuscular injections of	0	0	4.1	10.2
5648	0.5 c.c. of serum from infant ill with spasmophilia (whose serum P was 1.7 mg. % and Ca 7.4 mg. %).	0	0		
5457	Received daily intramuscular injections of	0	0	2.0	11.6
5462	0.6 c.c. of Na_2HPO_4 solution containing 15 mg. % P.	0	0		
	Averages			4.31	12.0

*See footnote 1, Table I.

Returning to the results of the five experiments recorded in Table I, the conclusion consequently must be drawn that the serums of rabbits which had received, five to ten days previously, approximately 1.6 mg. of irradiated ergosterol (200,000 international units of vitamin D) possessed very high antirachitic potencies. The question naturally arises at once whether or not this was due, partly or entirely, to the presence of vitamin D in the blood. It must, however, be kept in mind that the presence of irradiated ergosterol would not exclude the assumption that there might be a second substance produced by, and present with, vitamin D in the same serum.

The data recorded in Table III clearly answer these questions. Experiments I and II show that the rickets-curing substance can be partly removed from the serum by simple extraction with ether and, furthermore, that it is soluble in oil. Experiments III and IV demonstrate that this substance gradually loses its antirachitic potency if it is overirradiated with ultraviolet light. Finally, Experiments V and VI

show that the ultrafiltrate,* used in even larger doses than was the original serum, does not contain any rickets-curing substance.

TABLE III

EXPERIMENTS PROVING THAT THERE IS NO RACHITIC HEALING SUBSTANCE OTHER THAN VITAMIN D IN THE SERUM OF RABBITS GIVEN 200,000 INTERNATIONAL UNITS OF VITAMIN D BY MOUTH (20 C.C. OF VIOSTEROL) FIVE TO TEN DAYS PREVIOUSLY

EXPERIMENT	TREATMENT	RAT NO.	X-RAY HEALING AFTER		SERUM OF RATS†	
			EIGHT DAYS	TEN DAYS	P MG. %	Ca MG. %
I	From Rabbits 468 and 469* 15 c.c. of serum was extracted 8 times with 15 c.c. of ether. After evaporation of ether, residue was dissolved in 5 c.c. of wesson oil; 0.2 c.c. of this oil (equal to 0.6 c.c. of original serum) was injected daily intramuscularly in the rats.	5644	+++	+++	4.16	11.4
		5645	++	+++		
		5646	++	+++		
II	After extraction 8 times with ether, 0.6 c.c. of serum from Rabbits 468 and 469* was daily injected intramuscularly.	5639	+++	+++	3.86	12.0
		5641	++	+++		
		5643	+++	+++		
III	Serum from Rabbits 447 and 448* was irradiated 12 hr. with a Hanau mercury vapor quartz lamp at 46 cm. distance; 0.6 c.c. of this serum was daily injected intramuscularly in the rats.	5449	+?	++	3.88	12.0
		5450	+?	++		
		5451	+?	++		
		5461	+?	++		
IV	Daily intramuscular injections of 0.6 c.c. of serum from Rabbit 458* irradiated for 26 hr. as described in Experiment III.	5544	0	0	3.27	11.4
		5536	0	0		
V	Daily intramuscular injections of 0.6 c.c. of ultrafiltrate from serum of Rabbits 447 and 448.*	5454	0	0	2.88	10.8
		5458	0	0		
		5460	0	0		
		5463	0	0		
VI	Daily intramuscular injections of 1 c.c. of ultrafiltrate from serum of Rabbits 457 and 458.*	5548	0	0	---‡	9.8
		5549	0	0		

*The antirachitic potency of the untreated serum is recorded in Table I.
†See footnote 1, Table I.
‡Serum for determination was lost.

These results prove that the curative potency of this serum was due to a substance that had all the qualities possessed also by irradiated ergosterol: namely, it was soluble in ether and in oil; its antirachitic effectiveness was destructible by overirradiation;[11] and, because of its colloidal state in the lipoid fraction of serum, it was not ultrafiltrable. That overirradiation with ultraviolet light completely destroyed the antirachitic value of the serum makes extremely unlikely the possibility that a second substance was present, as do also the negative

*Filters were made with an 8 per cent collodion solution in glacial acetic acid. Ultrafiltrates were free from proteins, as shown by the sulphosalicylic acid test.

results obtained with serum ultrafiltrates. The conclusion must therefore be drawn that vitamin D itself produced the healing of the rachitic bone lesion and that, under the conditions described, it does not lead to the production of another substance capable of healing rickets or of increasing the phosphate content of the blood.

Having ascertained that the serum of rabbits to which 200,000 international units of vitamin D had been given contained, five to ten days later, considerable amounts of irradiated ergosterol, I thought it worth while to attempt to learn how long after its administration vitamin D circulates in vivo in the blood. Such experiments have not, so far as I know, been performed or reported in the literature up to the present time and should reveal the fate of vitamin D within the body in a more physiologic manner than do experiments in vitro.

The same rabbits were used for this group of experiments as for the previous group. Their blood was taken at intervals of one, three, six,

TABLE IV

SHOWING LENGTH OF TIME THAT VITAMIN D IS FOUND IN BLOOD OF RABBITS AFTER ADMINISTRATION OF SINGLE DOSE

RABBIT NO.	DATE 20 C.C. VIOSTEROL WAS GIVEN	DATE BLOOD WAS TAKEN	RABBIT SERUM		LENGTH OF TIME BETWEEN VIOSTEROL ADMINISTRATION AND TAKING OF BLOOD	RAT NO.	X-RAY HEALING AFTER		RAT SERUM*	
			P MG. %	Ca MG. %			EIGHT DAYS	TEN DAYS	P MG. %	Ca MG. %
445	12/ 6/34		4.8	16.2						
		12/12/34	4.8	17.4	1 wk.	5397	++	+++		
						5399	++	+++	5.5	14.4
						5401	++	+++		
		12/27/34	6.7	18.6	3 wk.	5446	++	+++		
						5447	++	+++	4.9	13.0
						5456	++	+++		
		2/23/35	5.1	13.8	11 wk.	5540	0	+	3.9	14.2
						5541	0	+		
448	12/22/34		4.1	11.0						
		12/28/34	7.8	17.0	1 wk.	5452	++	+++		
						5453	++	+++	5.4	13.6
						5459	++	+++		
		2/23/35	5.2	15.4	9 wk.	5537	0	+?	2.3	13.6
						5539	0	+		
457	2/19/35		4.2	15.4						
		2/25/35	4.3	16.0	1 wk.	5533	++	+++	4.0	---†
						5534	++	+++		
		3/30/35	4.8	14.2	6 wk.	5608	0	++		
						5609	0	+	8.5	10.4
						5610	0	++		
		5/ 3/35			11 wk.	5684	0	+?		
						5696	0	0		
						5698	0	0		

*See footnote 1, Table I.

†Serum for determination was lost.

nine, and eleven weeks following the administration of 200,000 international units of vitamin D (20 c.c. of viosterol in oil, corresponding approximately to 1.6 mg. of irradiated ergosterol), and was tested on rachitic rats in the manner already described.

The experiments summarized in Table IV show that, under the conditions prevailing, the serum of rabbits which had received viosterol was able to establish healing in rachitic rats in ten days, even if the blood was taken as long as from two to two and a half months after the administration of the vitamin. The first distinct decrease in the potency of the serum was noticed after six to nine weeks, and traces could be detected in one instance (Rabbit 445) after eleven weeks. In other words, rabbits weighing from 3,000 to 4,000 gm. needed from two and a half to three months to destroy or excrete 1.6 mg. of irradiated ergosterol (200,000 international units).

COMMENT

One finds in the literature no conclusive evidence whatever to support the view that there might exist a hormonal regulation of the phosphate metabolism, as is known to be the case for the calcium content of the blood. The studies presented here, in an attempt to approach the problem in a new way, have proved entirely negative. It must consequently be considered wiser to abandon a hypothesis that cannot be confirmed. It is better, I think, to see in irradiated sterols themselves the only substances the lack of which leads to rachitic hypophosphatemia and the presence of which elevates the inorganic phosphorus in the blood.

In which tissue vitamin D has its point of attack and by which chemical mechanism it increases the diminished inorganic phosphates in the blood of rachitic subjects must still be considered unknown. So far as the low phosphorus rickets in infants is concerned, I found[12] weighty evidence that suggests that the regulation of the intestinal absorption of phosphates does not explain the situation satisfactorily. Further studies on this subject are necessary and are in progress.

The fact that it has now been shown that vitamin D was circulating in the blood for at least two to three months after the administration of a single dose of approximately 1.6 mg. of irradiated ergosterol involves interesting new problems. It is superfluous to emphasize the clinical value of these observations to pediatricians who use vitamin D more or less routinely as an agent for preventing rickets in infants. It is known that damage can be done by overdosage of vitamin D,[13] and it is now shown through these studies that continuous administration may easily lead to an undesirable accumulation because of the apparently low rate of consumption.

The question whether the body destroys or excretes vitamin D cannot yet be decided. The work of Coppens and Metz,[14] who reported

that vitamin D is destroyed in vitro by blood and lung tissue, makes the assumption likely that it may be destroyed in vivo. The possibility that irradiated ergosterol may also be excreted through bile or through the intestinal wall must, however, be kept in mind. Studies on these problems are in progress.

SUMMARY

1. The oral administration to rabbits of 20 c.c. of viosterol in oil (200,000 international units of vitamin D, equivalent to approximately 1.6 mg. of irradiated ergosterol) led to an increase in the inorganic phosphorus content of the blood without correspondingly affecting the blood calcium content. This action took place about five days after the viosterol had been given and lasted until the tenth to the fifteenth day.

2. In order to learn whether or not this action might be due to the stimulating effect of vitamin D upon an endocrine gland, thus leading to the production of a phosphate hormone, the serum of these rabbits was tested on rachitic rats. The rabbits' blood was obtained five days after the viosterol had been given and was found to cure rachitic rats in from eight to ten days if 0.6 c.c. of the serum was daily injected intramuscularly.

3. No evidence was found, however, to justify the assumption that any substance other than irradiated ergosterol was present in this serum or was even partly responsible for its curative potency, because the rickets-curing substance of this serum was soluble in ether and in oil, was destroyed completely by overirradiation with ultraviolet rays, and was found not to be ultrafiltrable.

4. When viosterol was given by mouth to rabbits in a single dose corresponding to approximately 1.6 mg. of irradiated ergosterol, detectable amounts of vitamin D were found to be circulating in the blood for from two to three months.

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DEHYDRATION AND ACIDOSIS WITH CALCIFICATION AT RENAL TUBULES

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THIS communication reports the association of a clinical syndrome and pathologic picture which to our knowledge has not been described heretofore.

The clinical syndrome is characterized by: (1) a persistent dehydration in the absence of excessive diarrhea and vomiting and in the presence of adequate food, salt, and fluid intake; (2) a persistent hyperpnea associated with a sustained elevation of the serum chloride concentration and reduction of the serum bicarbonate content; and (3) deposits of calcium salts within and adjacent to certain renal tubules.

This condition is not simple to recognize as clinical states are frequently seen which appear quite similar until the disturbance of blood electrolytes has been carefully analyzed.

In infants acutely ill with diarrhea and vomiting, abnormal serum concentrations are frequently encountered because of a temporary functional inadequacy of the kidney due to fluid lack. In such cases the abnormal serum concentrations are quickly corrected by the proper administration of water, glucose, and saline. Occasionally chloride acidosis is encountered in dehydrated children coincident to the parenteral administration of physiologic saline. In the cases reported here, the persistent or recurrent hyperpnea and chloride acidosis in the absence of diarrhea, olyguria, and excessive saline therapy and in the presence of an adequate fluid and carbohydrate intake and the continued administration of sodium bicarbonate are strikingly unusual. Though specific gravity determinations on urine samples and other kidney function tests in these cases were not such as to give conclusive data concerning renal function, the nitrogen retentions and urine examinations for albumin and sediment did not indicate the presence of acute nephritis or inadequate functioning renal tissue. The absence of such pathology was confirmed at necropsy.

Calcification in the renal tubules has been observed in patients with the dehydration, hypochloremia, and alkalosis resulting from upper intestinal obstruction.[1-4] Cooke[4] suggested that renal changes in these cases were due to the alkalosis. We have seen such a case in a boy with upper intestinal obstruction and mesenteric thrombosis. Necropsy examination showed multiple calcium thrombi in vessels throughout

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the body and a heavy deposition of calcium salts in the renal tubules. Recently, Lightwood[5] has reported a group of six infants with gastroenteritis and vomiting in whom a similar deposition of calcium salts within the renal tubules was found at autopsy. Chemical analyses of the blood in his cases were not such as to give evidence concerning the existence of alkalosis or acidosis.

The picture presented by the four infants described here is striking enough to deserve special mention and characterization. Inasmuch as the dehydration in the infants demanded the parenteral administration of physiologic saline, a procedure which of itself may cause under certain conditions a chloride acidosis, the parenteral fluid therapy is reported in detail in the clinical records given below, so that the unique persistence of the chloride acidosis in these patients can be accurately appraised as a profound metabolic disturbance.

CASE REPORTS

CASE 1.—E. I., a baby girl of eleven months, was admitted to the hospital because of repeated vomiting for five months. She was a full-term infant, normally delivered, weighing 9¾ pounds, who from birth was fed a formula of cow's milk with added sugar. She never gained well and at six months of age weighed but 10 pounds. At that time she began vomiting, and from then until the time of admission she had vomited from one to four times daily. The vomiting was unrelated to food intake and was often projectile. From the age of two months the baby had taken a formula totalling at least 32 ounces of fluid a day and for the previous month had taken at least 40 ounces of formula as well as water which she took in "large amounts." She urinated very frequently and had always been troubled with constipation.

Physical examination showed a small and poorly developed child who was moderately malnourished and dehydrated. She had the appearance of chronic illness and was apathetic, showing little interest in her surroundings and often appearing stuporous. She weighed 12¼ pounds. Her temperature was 101° F. The throat was injected, and the tonsils were large and cryptic. There was marked hypotonia of the muscles with hyperflexibility of the joints. There was atrophy especially of the interosseous muscles of the hands and feet. The subcutaneous tissue particularly over the buttocks and thighs was firm and hardened as in sclerema, but the skin was not tense as in the sclerema occasionally seen in dehydrated infants to whom saline has been administered parenterally. The blood showed 85 per cent hemoglobin by Tallqvist test, a red blood cell count of 5,500,000 cells per cubic millimeter, and a white blood count of 20,000 cells per cubic millimeter. The urine was acid and contained no albumin and no cells or casts. The tuberculin and Wassermann tests were negative. Roentgenograms of the skull and long bones showed nothing remarkable other than an atrophy consistent with disuse.

On admission the signs of dehydration were so definite that the patient was given a hypodermoclysis of 125 c.c. of physiologic saline. She was then placed on a diet of milk, glucose, orange juice, and water. Since the child vomited only once during the first three days and the stools were normal, cereal, egg yoke, and cod liver oil were added to the diet. This diet was fairly well taken. On the fifth day, because of the continued semistuporous condition of the child, a lumbar puncture was done, and a clear fluid under no increased pressure was obtained. The total protein of this spinal fluid was 26 mg. per cent and the chloride 140 milliequivalents

per liter, an elevation of 15 meq. above the normal concentration. This increase in spinal fluid chloride was not remarked until two days later. The result, however, indicates that the blood chlorides were markedly elevated at a time when parenteral saline could not be held as a contributing cause.

During the sixth and seventh days, because of dehydration, the child received a total of 350 c.c. of physiologic saline by clysis and 100 c.c. of 10 per cent glucose by intravenous infusion. On the eighth day, though there had been no diarrhea, and only occasional vomiting, and though the urine output was not scanty (the child having voided six to nine times per day), the respirations became deep and the lethargy increased. The following day examination of the lungs revealed dullness and suppression of breath sounds on the right, and a roentgenogram showed a moderate amount of pulmonary infiltration. A sample of venous blood withdrawn under oil showed a serum bicarbonate content of 6 meq. per liter of serum, chloride of 134 meq. per liter (normal = 103-105), N.P.N. of 95 mg. per cent, and serum protein of 6.4 gm. per cent. The urine was acid and contained no albumin or formed elements. The infant continued to exhibit evidence of dehydration, and there was marked hyperpnea. The condition very rapidly grew worse. As soon as the results of the blood analyses were known, an attempt was made to administer sodium bicarbonate and glucose intravenously. Before this could be completed, respirations ceased.

CASE 2.—C. G., a ten-month-old baby girl, was brought to the hospital because she "had been sickly" and had failed to gain for four months. It was impossible to get a reliable history in any detail even with the aid of an interpreter. The child was born in Italy. She was reported to be healthy and to have nursed well. She was breast fed until eight months of age. Two months before admission the patient was placed on a cow's milk formula. Orange juice and cod liver oil were given in adequate, but not excessive, amounts for one month and then discontinued. The infant's bowels had been regular and stools of normal consistency. There had been no vomiting.

Physical examination showed a poorly developed and undernourished infant of ten months, weighing 11 pounds. The baby appeared small with a long narrow torso, slender extremities and marked frontal bosses. In spite of her weight she did not appear emaciated. The skin was dry, but the baby was not markedly dehydrated. Her temperature was 100° F. Both ear drums were full and injected, and there was a mucopurulent postnasal discharge. The lungs and heart were normal, and there was no abnormality in breathing. There was a marked hypotonia of the muscles. The blood pressure was 100 systolic over 60 diastolic. The tuberculin and Wassermann tests were negative. The urine was acid and contained no albumin but showed a few red and white blood cells and granular casts in uncentrifuged specimens. Roentgenograms revealed nothing remarkable other than increased density at the ends of the long bones as seen in retardation of growth.

The child was placed on a formula of whole milk, karo, and water, to yield about 45 calories per pound, and was given orange juice and cod liver oil. Her bowel movements were regular and normal in consistency, and she voided from six to twelve times daily. On the eighth day following admission she had lost six ounces in weight and, though there was no significant elevation in temperature and no vomiting or diarrhea, she gave the appearance of a severely dehydrated child. There was a moderate hyperpnea. At this time a sample of venous blood withdrawn under oil contained 11 meq. of bicarbonate, 121 meq. of chloride, and 138 meq. (normal = 135-140) of sodium per liter of serum. A phenolsulphonephthalein renal test gave 12 per cent excretion in 55 c.c. of urine during a two-hour period. An intravenous infusion of 130 c.c. of 10 per cent glucose plus 2 gm. of sodium bicarbonate and a clysis of 200 c.c. of physiologic saline were given. One quar-

ter of a dram of sodium bicarbonate was given twice daily by mouth. Two days later the venous blood showed an N.P.N. of 30 mg. per cent and a serum sodium and chloride of 141 and 131 meq. per liter, respectively. The child's respirations were rapid, dyspneic, and irregular. The following day signs of pulmonary infiltration developed. The temperature rose to 108° F. before death.

CASE 3.—D. Y., a baby girl, seven weeks old, was admitted to the hospital because of failure to gain throughout life and vomiting during the preceding five days. She was a full-term, 7½-pound baby, normally delivered. She had been breast fed for three weeks and then, because of "influenza" of the mother, had been on a dried milk, and later a condensed milk, formula. Ever since weaning the patient had been constipated and had been given "one teaspoonful of milk of magnesia almost daily." The baby had always acted hungry but seemed to tire easily at feedings and never succeeded in taking much of the formula at a time. When first seen she was malnourished, showed some loss of elasticity of the subcutaneous tissue, was listless, and made only ineffective nursing efforts. No physical abnormalities were found. The urine contained the slightest trace of albumin and rare red and white blood cells. Roentgenograms showed increased density at the metaphyseal margins, indicating retarded growth. There were no calcified areas in the region of the kidneys.

Following admission the infant was placed on a milk, sugar, and water formula and was given orange juice, glucose and physiologic saline between feedings. At the end of three days the child appeared more dehydrated than at entry although she had neither vomited nor had diarrhea. She had voided ten to twelve times per day. Her temperature, which was normal over the first two days, was 101° F. on the third day, and her respirations were rapid. There was a pharyngitis, but there were no signs of pulmonary infiltration by physical or x-ray examination. Because of the dehydration she was given an intravenous infusion of 70 c.c. of 10 per cent glucose and a clysis of 150 c.c. of physiologic saline. During the next two days hyperpnea became apparent, and on the sixth day this evidence of acidosis became marked. The temperature fluctuated between 105° and 98° F. On this day, analyses of venous blood withdrawn under oil showed a marked acidosis due to an abnormally high serum chloride concentration. The serum concentrations determined on this and subsequent days are enumerated in Table I.

The child's course for the next ten weeks was characterized by languor, persistent hyperpnea, and evidence of dehydration, and by an irregular fever with gradually developing signs of pneumonia. Table I indicates the degree of the acidosis, the persistence of the elevated serum chloride concentration, and the serum sodium concentration. The serum N.P.N. was not elevated, and a phenolsulphonephthalein test showed 40 per cent excretion in two hours. Therapy consisted of large amounts of water and sodium bicarbonate by mouth, which the baby took well without vomiting, and repeated intravenous administration of glucose, sodium bicarbonate, and whole blood. The parenteral fluid therapy is detailed in Table I. There was persistent constipation. Feedings of milk, corn syrup, and water giving 50-60 calories per pound, were fairly well taken except terminally. On the twenty-first day in the hospital the baby had a temperature of 106° F. and a convulsion. Respirations were slow and shallow. The urine was alkaline. The daily 1.5 grams of sodium bicarbonate by mouth were discontinued as it was felt that the sodium administration might have been carried so far as to produce tetany from alkalosis. Unfortunately, serum bicarbonate and calcium concentrations were not determined at this time. However, hyperpnea and chloride acidosis (Table I) were again marked on the twenty-fifth day, and the oral administration of sodium bicarbonate was resumed. On the sixty-seventh day the serum bicarbonate was 11, chloride 123,

sodium 143 meq. per liter and pH 7.10. At this time a urine specimen collected over a period from one hour before to one hour after the collection of the blood sample showed urinary sodium and chloride concentrations, respectively, of 107 and 82 meq. per liter when the rate of urinary excretion was 0.3 per c.c. per minute. Hence it would seem that the urinary excretion was not such as to correct the chloride acidosis effectively. The baby died on the seventy-sixth day after admission.

TABLE I

SERUM CONCENTRATIONS AND PARENTERAL FLUIDS. CASE OF D. Y.

DAY	MEQ. PER L.			MG. PER CENT			GM. PER CENT	pH	PARENTERAL THERAPY C.C.
	HCO_3	Cl	Na	Ca	P	N.P.N.	PROTEIN		
3									70 A*
									150 D§
6	9	140	148	10	5.5	30			
8	14							7.25	
13	8	130							
16	14	123							
19	16	120							
25	10	123	135			33	7.9	7.10	150 B†
26									70 E‖
32	10	124	140						
35									100 E
36									90 B
39	9	124	137						90 B
40									90 B
46	10	128	138						
54	11	123	137						
66									100 C‡
									180 D
67	11	123	143			22		7.10	100 E
68									100 C
69									100 C
70									100 C
71	20	94							100 C
72									100 C
73									100 C
74	18	104	133						
75									70 E

*A, solution of 10 per cent glucose.
†B, solution of 10 per cent glucose containing 1 to 3 per cent sodium bicarbonate.
‡C, solution of 5 per cent glucose containing 1 to 3 per cent sodium bicarbonate.
§D, physiologic saline given subcutaneously.
‖E, citrated whole blood.

As can be seen from Table I there was always a marked lowering of the serum bicarbonate and, except terminally, an elevation of chloride. The serum sodium never reached abnormal heights. Altogether in the seventy-six days of hospitalization some 80 gm. of sodium bicarbonate were given by mouth and 15 gm. intravenously.

CASE 4.—L. H., a two-week-old male infant, was admitted to the hospital because of vomiting and diarrhea. He had been a normal baby during the first week of life. Vomiting, which began the beginning of the second week, was fairly frequent but not definitely projectile. There was a loose but not watery stool passed after each feeding. On admission the outstanding feature of the physical examination was the extreme malnutrition and dehydration. The eyes were sunken, the skin was dry, and there was marked loss of subcutaneous tissue. The mouth was layered with typical thrush. Heart, lungs, and abdomen were normal. He weighed 5 pounds compared to his birth weight of 6.5 pounds. The red blood count was

5,250,000 per cubic millimeter, the white count 25,000 of which 70 per cent were polymorphonuclear cells, and the hemoglobin was 115 per cent of normal. The urine was acid and contained many cellular casts and crystals, occasional red and white blood cells, and no albumin. The Wassermann and tuberculin tests were negative. Roentgenograms of the chest, extremities, and abdomen showed no abnormality. There was no calcification evident in the kidney region.

Venous blood withdrawn under oil showed on admission a serum chloride concentration above normal, while the serum sodium was below a normal level (Table II). The N.P.N. was markedly elevated. The course of the illness and parenteral therapy are tabulated in Table II.

TABLE II

SERUM CONCENTRATIONS AND FLUID INTAKE. CASE L. H.

DAY	SERUM CONC.						FLUIDS	
	MEQ. PER L.			MG. PER CENT		GM. PER CENT	PARENTERAL C.C.	PER OS
	HCO_3	Cl	Na	Ca	N.P.N.	PROTEIN		
1		114	128		150	7.4	60 A*	
							100 D	
2							50 E	1.5 oz. f.f. milk q. 3 h.
							100 C	
							85 D	
3								1.5 oz. f.f. milk q. 3 h.
4	12	126			31		100 B	2 oz. f.f. m. q. 4 h.; 7 oz.
							120 D	10% glucose and N. saline āā
5								2 oz. f.f. m. q. 4 h.; 7 oz. 10% glucose and N. saline āā
6							100 B	2 oz. f.f. m. q. 4 h.; 7 oz.
							120 D	10% glucose and N. saline āā
7	6	132			48	6.6	200 B	2 oz. f.f. m. q. 4 h.; 15 gr.
							240 D	$NaHCO_3$ in O.J. q. 4 h.
8	22	124	160	8.0			70 A	2 oz. f.f. m. q. 4 h.; 5 gr.
							135 D	$NaHCO_3$ in O.J. q. 4 h.
9							70 A	2 oz. f.f. m. q. 4 h.; 5 gr.
							135 D	$NaHCO_3$ in O.J. q. 4 h.
10							50 E	2 oz. f.f. m. q. 4 h.; 5 gr.
							600 C	$NaHCO_3$ in O.J. q. 4 h.
11		98	123	6.3	47	4.3	10 F†	2 oz. f.f. m. q. 4 h.; 5 gr. $NaHCO_3$ in O.J. q. 4 h.
12							50 E	Breast milk 2 oz. × 4 Skim milk 1.5 × 2
13							615 G‡	Breast milk 2 oz. × 4 Skim milk 1.5 × 2
14		126		10.5		5.4		Breast milk 2 oz. × 4 Skim milk 1.5 × 2

*A, B, C, D, E, solutions as given in Table I.
†F, 10 per cent calcium gluconate.
‡G, Hartmann's lactate Ringer's solution.

The essential features of the illness were persistent dehydration and hyperpnea. The day following admission the stools became watery and varied from none to ten per day, but the fluid thus lost never seemed enough to explain the dehydration. The high N.P.N. at entry was evidently due to a diminished kidney function associated with the dehydration since it fell almost to normal on the administration of parenteral fluids. On the eighth day alkaline therapy resulted in elevating the

serum sodium to 160 meq. per liter with a resultant increase of the serum bicarbonate to a low normal, but the serum chloride at this time remained elevated. On the eleventh day following 600 c.c. of 5 per cent glucose containing 2 per cent sodium bicarbonate given by continuous intravenous drip over a period of twenty hours, the patient had a generalized convulsion. This, in spite of the transfusion given on the tenth day, evidently was associated with a dilution of the blood by the

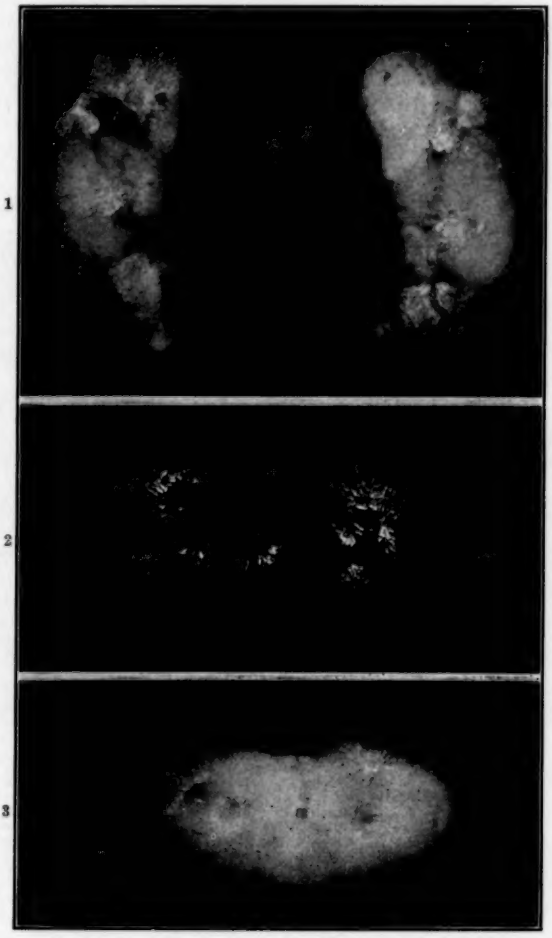

Fig. 1.—Reproductions of roentgenograms of kidneys at autopsy showing the opaque deposits outlining the pyramids.

intravenous therapy as indicated by the drop in serum protein concentration from 6.6 gm. per cent to 4.3 and serum calcium from 8.0 mg. per cent to 6.3. With this dilution the serum chloride fell to slightly below the normal level, while the serum sodium dropped so far below its normal concentration that the bicarbonate could hardly have been elevated (Table II). Intravenous calcium gluconate, calcium lactate by mouth, and a transfusion corrected the low serum calcium and raised the

serum protein concentration. Since the dehydration in the presence of the gastrointestinal disturbance demanded more fluids than seemed advisable by mouth, a continuous clysis of Hartmann's lactate Ringer's solution was started on the thirteenth day. The infant grew weaker and died on the fifteenth day of hospitalization.

NECROPSY FINDINGS

The essential pathologic findings in these infants at necropsy were in the lungs and kidneys. An acute terminal pneumonia was present in all four. An otitis media was present in two. Except for a variation in the degree of the calcification the kidneys were strikingly similar and may be characterized as follows:

The kidneys were of approximately normal weight for the age. The capsules stripped with ease revealing smooth, pale surfaces. Sagittal

Fig. 2.—The central tubule shows the initial lesion. There are deposits of calcium about the basement membrane but none in the tubular epithelium. Around the tubule there is an increase in fibrous tissue. Several normal tubules are also included. Hematoxylin-eosin stain after Regaud fixation, ×300. Case 2.

section revealed a pale cortex of normal width well demarcated from the medulla. The medulla ranged from pink to gray in color. Throughout the medulla, but particularly at the periphery of the pyramids, small bristlelike deposits barely visible to the naked eye were present.* These deposits outlined the limits of the pyramids. On passing a knife over these a gritty resistance was encountered. The calices, pelves, and ureters showed nothing remarkable.

X-ray films of the kidneys at necropsy showed a diffuse deposition of calcium salts throughout the medulla (Fig. 1).

*In case L. H. no deposits could be noted with the naked eye.

On microscopic examination sections stained by the von Kossa technic gave positive reactions for calcium. The earliest lesions showed calcium deposition within the walls of the collecting tubules between the basement membrane and the epithelial cells and within the connective tissue surrounding the tubules. Frequently the deposits of calcium within the walls of the tubules resulted in an inpouching of the epithelium, a narrowing of the lumen, and degeneration of the epithelial cells. The photomicrographs of Figs. 2 and 3 illustrate these lesions. Many tubules were irregular in shape and contained masses of amorphous calcium in which rings of organic matrix could be recognized. The collecting tubules were most often involved, but deposits of calcium were rarely found in the proximal convoluted tubules.

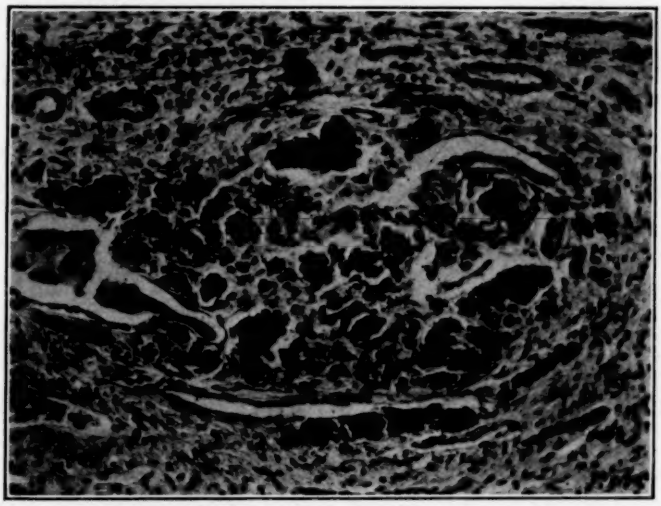

Fig. 2.—A more advanced stage of the pathologic lesion. There are masses of calcium, remnants of tubules, and fibrous tissue in a heterogeneous mass. At the left there is a collecting tubule which is dilated and filled with a hyaline cast. The long tubule near the bottom of the figure presents a calcium deposit beneath the basement membrane similar to that shown in Fig. 1. This indicates the progressive nature of the lesion. Some adjacent tubules are normal though there is an increase in the interstitial connective tissue. Hematoxylin-eosin stain after Regaud fixation, ×300. Case 2.

Large calcified deposits adjacent to atrophic collecting tubules were often accompanied by foreign body giant cells and surrounded by dense connective tissue derived from the stroma of the kidney, indicative of a process of at least several weeks' duration.

No inflammatory cell infiltration or evidence of nephritis accompanied these lesions. The vascular system throughout the bodies showed no evidence of calcification, nor were areas of calcification encountered elsewhere. The parathyroid glands were normal.

COMMENT

Only one of the five patients had definite sclerema. This seems worthy of particular note since the sclerema occasionally seen in dehydrated infants is frequently associated with an elevated serum chloride concentration in the absence of any demonstrable renal pathology.

Hypotonia occurred in a striking degree in two of the four infants. It was not present, however, in a remarkable degree in the two youngest infants who were two and seven weeks of age, respectively. Hypotonia is hard to evaluate and is not usually of diagnostic significance, but in two of these cases it was unusually marked. More commonly a chronically malnourished infant with severe infection is likely to be hypertonic rather than the opposite.

In each of the infants there was evidence of first a respiratory infection and terminally a pneumonia. It is our opinion that these were wholly secondary manifestations such as are seen as terminal events in infants with severe nutritional disturbances of any etiology.

The microscopic picture of the renal lesions indicates that the calcium is first deposited between the tubular epithelium and the basement membrane of the tubule. The smallest deposits were globular, and the deposits never took the form of a layer surrounding tubules or blood vessels in the stroma, even in the largest accumulations.

Calcification frequently occurs in necrotic tissues. In mercury bichloride poisoning, the calcification is secondary to necrosis of the epithelial cells of the tubules, notably those of the convoluted tubules. The calcium salts are deposited first within the necrotic cells themselves, and the early sequences as well as the final picture are entirely different from those of the kidneys under discussion. There was no evidence in any kidney of the infants reported here that calcification was secondary to degeneration of any renal element. It may be pertinent to suggest that the calcium deposits were in locations traversed by calcium salts during normal renal function.

Though an alkalosis from chloride loss due to vomiting may have occurred at some time in these infants, their courses while under observation gave no evidence of a simultaneous alkalosis and dehydration that might have contributed to calcification in the renal tubules. Since no alkali was given one of our patients, the calcification would not seem to have resulted from alkaline therapy.

The absence of any histologic evidence of parathyroid hyperplasia or calcification elsewhere in the body indicates an etiology of the renal calcification other than hyperparathyroidism.

We have observed the association of diffuse calcification at the renal tubules and persistent hyperchloremia and acidosis in two patients* whose ages, clinical histories, and pathology were different from the cases reported here. Though this association requires fur-

ther study, its occurrence in patients whose pathologic pictures are so different in other respects suggests a relation between the renal lesion and the metabolic disturbance.

A wider recognition of this condition may lead to an understanding of its etiology and a treatment that is more successful than the symptomatic one given our patients.

SUMMARY

We report a group of four infants and one child who showed a strikingly similar syndrome characterized by persistent dehydration, acidosis with hyperchloremia, and extensive diffuse deposits of calcium salts in and around the renal tubules.

*M. L. was a ten-year-old boy admitted to the hospital because of weakness and stunted growth. He developed "rickets" at one and a half years of age. At four years he fell and broke his right femur and from that time failed to grow normally. Weakness, polydipsia, and polyuria became marked during the preceding two years. Examination showed an underdeveloped and moderately emaciated boy who had difficulty in raising himself from the prone to standing position. The urine contained varying amounts of albumin and casts and numerous red and white blood cells. Its specific gravity was limited to 1.009. The blood pressure was 110 over 75. Roentgenograms showed general osteoporosis and broad osteoid zones at the ends of the long bones, as seen in rickets tarda or renal rickets, and diffuse calcium deposits in both kidneys. Phenolsulphonephthalein excretion was 70 per cent in two hours. Serum analyses showed normal serum calcium, low inorganic phosphorus, elevated chloride, a low bicarbonate, normal N.P.N. concentrations, and a phosphatase concentration of 1.0 (normal 0.3). The low serum phosphorus level and the adequacy of the kidney function were not consistent with renal rickets.[5, 7] Roentgenograms showed no cystic areas in the bones. Moreover, inasmuch as the urinary excretions of calcium and phosphorus were but slightly above the normal levels, balance data did not support the diagnosis of hyperparathyroidism without a severer kidney insufficiency than seemed present in this case.[8] Nephrolithotomy was attempted on one kidney, but the calcification was so diffuse and intimately associated with the renal parenchyma that its removal was impossible without excessive damage to the renal structure. The opaque material removed was shown on analysis to be a calcium phosphate carbonate compound of the composition of bone. During eight weeks the serum chloride varied between 124 and 114 meq. per liter and the serum bicarbonate never exceeded 16 meq. per liter. The patient left the hospital against advice before a diagnosis was made.

The second case was in a patient observed through the kindness of Dr. Fuller Albright at the Massachusetts General Hospital. He was a young man, twenty years old, who had had hyperparathyroid disease due to an adenoma which had been removed surgically. Diffuse calcification throughout the pyramids of the kidneys was associated with a hyperchloremia and acidosis.

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Critical Review

ALLERGIC DISEASES

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CRITICAL reviews, as the term would signify, allow the writer to interpret reports and comment according to his own ideas. It is intended then that the criticisms be stimulating to discussion and further inquiry and in no sense an adequate judgment. The reader may refer to the three preceding annual reviews[1] for the writer's "biased opinion." It is inevitable, with the growth of interest in allergy, that many articles may be overlooked.

A most interesting book by Wodehouse[2] has been published during the past year. It deals with pollen and its significance in hay fever and gives a more extensive discussion of the morphology of pollen grains and the results of pollen surveys than is found in the general texts on allergy. However, much of the discussion in the book is based on early reports which might be considered out of date, and scant attention is given to the pollen problem west of the Mississippi. Gay's[3] impressive volume, *Agents of Disease and Host Resistance*, includes chapters on Anaphylaxis[4] and Allergy.[5] The latter compiled by David and Beatrice Carrier Seegal are particularly valuable in their discussion of bacterial allergy. Mention should also be made of a German text on allergy by Hugo Kammerer,[6] which escaped attention in last year's review and which the reviewer has not yet been able to examine.

The experimental approach to a study of allergy has received increasing attention. Brunsting and Bailey[7] successfully induced contact dermatitis in guinea pigs. As mentioned previously, the production of primrose dermatitis was successful in Bloch's experiments[8] on human beings. Much of the study of nickel dermatitis has been made on animals, but the induction of contact dermatitis in experimental animals by the use of oil extract is new and perhaps, by some, unexpected. Bernstein[9] combined horse serum with pollens and found that by injection guinea pigs were made susceptible to anaphylactic response from shock injections of pollens. Somewhat similar fortification phenomena have, of course, been observed in other fields.

One of the most important contributions to the theoretical understanding of allergy is the report of the Dutch workers, Benjamin and his associates.[10] These investigators sought an explanation for the fact that removal of the protein from pollen extracts, by filtration or digestion, reduced but did not eliminate the skin-test potency of the filtrate. Choosing the simpler filtration method, they found that when the filtrate was united with substances of large molecular size, but inert themselves, a fortified or intensified skin test was obtained. A

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second filtration left the more active skin-test fraction in the residue. Substances which they tried for this fortification effect on ragweed filtrate were of varied source and type such as human ablumin, aleuronat, casein, gelatin, polysaccharides, and amino acids. The polysaccharides were ineffective, save for glycogen, which is obvoiusly more complex than ordinary polysaccharides. Tapioca, which has been used to "catalyze" the production of diphtheria antitoxin, was a good activator. The amino acids as a group were inert except for leucine, glycine and cystine, which were activators in one instance. They suggested in relation to skin proteins a parallel with enzyme action where there also are noncolloid activators. In general, however, they believe the activation results from the binding or adsorbing of the small "free" groups in the initial filtrate with large (usually protein) molecules, somewhat like the action of protective colloids. If the contention of these workers is correct and the activity of skin testing substances depends on a protection against decomposition in the skin of the small groups by linkage with large molecular substances, an explanation for many of our problems is at hand. There will, of course, be further inquiry into the nature of the linkage, adsorption, or binding, and the comparison of the effect of superimposing the small fraction on a site previously used by the activator alone to see if the binding will take place in vivo. While the authors avoid finality in opinion, they present evidence supporting more than localization or dispersion phenomena. It is perhaps mere conjecture, but beyond the skin test study one wonders if in the field of treatment combinations with human albumin warrant trial and whether, as with toxoids, a combination of pollen filtrate with alum would be effective. The ultrafiltered pollen extract is less effective than unfiltered extract in treatment of ragweed hay fever according to the preliminary report of Spain and Sammis.[11] If then the residue with its large molecule linkage is still more effective in treatment, perhaps artificial linkages may improve the natural product. It would also be of interest to know if any part of the immediate passive transfer reactions, such as have been described by Gay[12] and others, involves a fortification of the pollen extract as well as a transfer of "reagins."

Osgood and Hubbard,[13] in a less comprehensive report than that of the Dutch workers, found that filtering pollen solutions through a Seitz filter reduced the protein nitrogen and the skin reaction potency of the filtrate. As a measure of the skin excitant they found nitrogen determinations by the trichloracetic acid method better than total nitrogen or phosphotungstic acid precipitation determinations.

Cooke, Stull, Hebald, and Barnard,[14] in their continued study of the relationship of giant and low ragweed, found that extracts of the two ragweeds, when standardized in protein nitrogen content, gave comparable skin tests and constitutional reactions regardless of the source of the pollen. Reactions and constitutional response by passive transfer were greater with the low ragweed so that differentiation might possibly be made with that technic but not by direct test.

Caulfeild, Brown, and Waters[15] have found by passive transfer studies evidence of more than one active substance in the same ragweed pollen. According to their interpretation of the results, there is more than one specific reagin. Caulfeild[16] has also made a preliminary report on the use of pollen carbohydrate as a therapeutic agent for pollen asthma. Interest in specific carbohydrate fractions in bacterio-

logic research has led to therapeutic application. The author found that patients treated with this carbohydrate fraction seemed to require less epinephrine for the relief of attacks than control patients. The author admits the difficulty of comparison of patients and evaluation based on symptomatic response.

Skin testing phenomena have always presented many difficulties in interpretation. Bowman[17] called attention to the necessity of using parallel sites on the arms if comparisons are made in routine tests. This, of course, has been recognized previously and is part of the phenomenon repeatedly emphasized by Alexander.[18] Grow and Herman[19] tested 150 apparently normal individuals, of whom 83 gave positive responses to one or more allergens. The reviewer feels that this proportion would be very good among known allergic individuals. Similar findings have been subject to comment in previous reviews, but they probably deserve emphasis not only because of the delicacy of the test, especially in children, but also because of the lack of parallel with clinical symptoms. The skin test is not an infallible guide.

Hubbard and Osgood[20] determined the protein content of allergen extracts by various methods. The reviewer finds himself in hearty accord with their belief that standardization of the less known allergens is unwarranted. Anderson[21] expresses the rather unorthodox opinion regarding pollen extract preparations, namely, that small doses of pollen mixtures are more efficacious in treatment than concentrated amounts of the chief offending pollens. It is usually customary to give the extracts of pollens according to the indication of the skin test and the most predominant pollens in the local survey. The results have been interpreted as reflecting an increased tolerance from graded injection beyond the usual amount encountered by exposure. Anderson, however, believes that the small mixtures are of value because they resemble the mixtures which the patient inhales. This apparently questions the specificity of selected pollens and does not recognize careful pollen counts. However, individual variations make didactic statements difficult.

Biederman[22] contends that patients having positive skin tests to pollens present in a season during which they have no clinical symptoms may (in 5 per cent) develop symptoms. Hence, he advocates inclusion of these pollens in hyposensitizing. He believes that patients will show improvement and loss of skin reactions with such a program. The effect of treatment on the skin tests is controversial, and the reviewer can cite several instances where Biederman's conclusions might not be substantiated. As for the results of hay fever treatment, Vander Veer and Clarke[23] find that permanent relief can be expected in 50 per cent of those treated and is most obvious in those having five to eight years of treatment. They feel that successful seasonal treatment favors permanent relief and that the pollen content of the air affects both this and the seasonal relief.

The pollen surveys of Pittsburgh[24] and San Francisco[25] are welcome contributions to this phase of allergy. The old controversy concerning the effect of treatment on the skin test is the subject of a report by Markow and Spain.[26] These authors report, in agreement with Coca,[27] little change after one or two years' perennial treatment. Such variations as were found, they suggest, may be due to loss of potency of the extracts and predicate need of renewal of the extract during the perennial treatment.

The observations reported by Furstenberg and Gay[28] are a greater contribution. The authors noted a purplish cyanosis at the site of the injection of the allergen by obstructing circulation to the skin. The characteristic wheal appeared when the circulation was restored by release of the tourniquet but was less intense than when the circulation had not been obstructed. The tourniquet application apparently made for less dispersion or greater fixation of the reagin with passive transfer. This conclusion was based on the earlier observation of exhaustion of the control site as compared with the experimental site. They hope to show by the use of dyes that perhaps the erythematous flare will involve the dye and differentiate the erythema from the wheal formation. Such observations may shed more light on Lewis'[29] theory regarding urticaria.

Dienes and Simon[30] report the flaring up of injection sites in sensitized guinea pigs. Phenomena of this sort have been observed in serum sickness. Further study of Schwartzman's phenomenon will prove valuable in differentiating specific and nonspecific skin responses.

Foshay[31] describes two distinct reactions encountered in testing with antiserums, one a bacteria-specific response, the other dependent on serum sensitization. He used antiserum for tularense and brucella infections. From this observation it would seem less confusing to test for serum sensitivity with horse serum rather than with the antiserum.

Seegal, Khorazo, and Mehlman,[32] by the term "local serum sickness in man," described the effect of repeated intracutaneous injections of 0.1 c.c. of foreign serum. They used sheep, horse, rabbit, and beef as sources and found the serum of the first two more effective in producing the local response in the reinjected site. Purified globulin was less effective than was the unaltered serum. No correlation could be made with the effect of previous parenteral injection elsewhere than at the local site. The question of the slow diffusion from intracutaneous injection and the question of the Forssman antigen effect were raised. There were delayed and hastened reactions and variations in the same individual which suggested multiple rather than single antigens.

A clinical instance of anaphylactic shock was seen by Freedman.[33] The patient, an asthmatic individual, had been given toxin-antitoxin twenty days prior to the fatal injection. Asthma and urticaria had followed the toxin-antitoxin injection. Twenty days later, an intracutaneous test with horse serum used to detect serum sensitivity proved fatal. The reviewer has been told that such episodes are rare, but this occurrence none the less breaks down some of the differentiating features of allergy and anaphylaxis.

The importance of the skin in both allergic and immunologic mechanisms has continued to interest investigators. Kern, Crump, and Cope[34] reported the immunization of allergic and nonallergic individuals by intracutaneous injection of alum-precipitated toxoid. According to them, 0.1 c.c. of this material given intracutaneously is as effective as ten times that amount given subcutaneously. They claimed that unfavorable reactions are less frequent and could well be controlled by tests with the small amounts of toxoid given subcutaneously. This latter method, it will be recalled, was advocated by Thelander[35] for the administration of toxoid to older individuals. The intracutaneous injection would be slower of absorption and the use of a

tourniquet, as advocated by many allergists, could further delay generalized reactions. However, from the standpoint of immunity, despite current acceptance of the Schick test as a guide, such reports might be even more valuable if a check on blood titer were made, as for example by the Kellogg test.

Efron and Silverman[36] obtained positive skin reactions to filtrates of the dysentery bacilli. The skin response was greater to the specific organism of the patient than to other members of the dysentery group of organisms.

Lamb, Anderson, and Nerb[37] claim from their observations of the skin test with filtrates that streptococci are responsible for atrophic arthritis and that they are of value therapeutically. Although different strains of the organism in various foci may be etiologic, the authors recommend autogenous filtrates for which they claim better results than with the vaccine. The significance of positive skin tests to streptococcic filtrates is exceedingly difficult for the reviewer to evaluate. The study of skin tests to streptococcic filtrates made by the Kreuger method has made the reviewer rather skeptical of the interpretation at the present time.

Feinberg and Little[38] have undertaken a most difficult but thorough search for the relation of microorganisms to allergy. Testing 600 allergic patients to dry powdered yeasts, they found 65 who gave positive reactions. Reactions to the entire group of yeasts were the rule, and in some instances reactions to fungi were obtained. Adequate controls and passive transfer verified the skin test interpretation. Interesting information was given regarding common sources of yeasts, but the authors avoided a didactic clinical interpretation. A second report[39] by these authors dealt with the daily mold spore content of the air. Exposure of Sabouraud's medium on Petri dishes enabled the counting of spore formation for a twenty-four-hour exposure of the plates. A seasonal trend for *Alternaria* and *Hormodendrum* was noted, which apparently parallels the clinical symptoms of patients sensitive to molds. The Chicago survey showed greater spore development in the warmer months even though the spores are present throughout the year. A greater pollen count occurred coincidentally with the high spore count. The report stimulates numerous questions as to the rôle of humidity, urban versus rural factors, and air content of inert particles such as soot, etc. Biederman[40] reported four patients with allergic manifestations and positive skin tests to yeast. The author advised testing with yeast allergen routinely.

Pennington,[41] in studying trychophytin and monilia in relation to allergy, offers further confirmation of Sulzberger's early reports. The patient reported by Tomlinson[42] had epidermophytosis and gave direct skin tests to six different types of trychophytin extracts. The reactions were without the delayed component described by Sulzberger and Kerr.[43] Tomlinson obtained successful passive transfer but could not demonstrate precipitins (in rabbit experiments). Of the six extracts, the broth culture extract was most potent in polysaccharide and most effective in skin testing.

The nature of house dust allergen, which has been subject to so much controversy, may be somewhat nearer understanding from the investigations of Cohe nand his coworkers.[44] The allergen apparently develops in cotton linters under conditions which exclude the possibility

of contamination with other allergens. Bacterial or mold action is not responsible for the aging process which produces the allergen. Further studies may show the factors in the aging of linters, kapok, and feathers, but at least the development of the allergen for cotton has been rather ingeniously traced. Spain and Newell[45] have reported their use of cellophane as a membrane for ultrafiltration of house dust extract. Many workers are probably familiar with cellophane as a membrane for dialysis.

This year, as compared with past years, has not been marked with efforts to recognize constitutional features of the allergic individual. In a previous review[46] attention was called to the finding of hypochlorhydria in asthma emphasized by the British. An opinion was expressed at that time that perhaps this finding would be shown as secondary rather than causal in its relationship. Such would now be the interpretation of the report by Gillespie.[47] He found hypochlorhydria common under fifteen years of age, perhaps related to excess mucus production and without relation to sensitivity. Disappearance of the hypochlorhydria was noted with clinical improvement. Continuing their studies of the relation of the adrenal gland to allergic phenomena, Cohen and Rudolph[48] tried the effect of adrenal stimulation by strychnine. The hypertonicity which resulted quite overshadowed the possible benefit of epinephrine production. The experiment, though of interest academically, is not recommended as being clinically sound. Not adrenal but ovarian dysfunction is suspected by Goldberg[49] as the inciting constitutional factor in his report of climacteric hypersensitiveness to sun and effort. Follicular hormone therapy brought subsidence of the symptoms. It is difficult at the present time to limit the possible inciting or precipitating factors of a constitutional nature. Operations and endocrine upsets are perhaps best considered shock effects. Infections of various types may be similarly responsible as for example the instances of cold urticaria following measles described recently by Kobacker and Parkhurst.[50]

Matzger[51] has called attention to relief of asthma by administration of intravenous glucose. Wegierko,[52] on the other hand, suggests that induction of hypoglycemia is beneficial. Neither phase of metabolism should be stressed until both are better understood. The reviewer has seen both types of treatment with varying results.

There was a time when without sufficient indication tonsillectomy and antrum irrigations were urged for relief of asthma. Such relief of asthma as was obtained was temporary and was probably the effect of nonspecific shock together with anesthesia. Local anesthesia, particularly that used for antrum irrigations, has long been known to thwart an impending asthmatic attack. Last year mention was made of Coca's report[53] of improvement following surgical measures. And, although anesthesia has been recently advocated by Kahn[54] for semipermanent relief, there has been a swing of sentiment against tonsillectomy in asthmatic patients. The statistics of Kaiser[55] have done much to check the enthusiasm for tonsillectomy, though the reviewer feels that such statistics on mass observations do not necessarily compare with the information gathered from more intimate studies. Bullen[56] has emphasized the aggravation of asthma following tonsillectomy. It is the opinion of the reviewer that surgical procedures may moderate the symptoms of some patients and aggravate the symptoms

of other patients. On such a basis tonsillectomy is neither indicated nor contraindicated by the presence of asthma. Indications depend upon the observation of infection and the appearance of the tonsils. The opponents of tonsillectomy mention the possible "autodesensitization" and filtration by the intact tonsil. Wholesale acceptance of this theory seems to the reviewer a considerable risk to the general health. Although tonsillectomy has been unquestionably overdone, this newer tendency seems extremely reactionary.

The study reported by Ellis[57] concerned erythrocyte sedimentation in allergic disease. He inclines toward the theory that there is an increased suspension stability of the red cells, and the question might be raised as to whether the "spread" of "normal standards" includes instances of minor allergy.

The suggestion made by Cooke and his coworkers[58] that the blood of treated hay fever patients may contain an immune body is of both theoretical and clinical value. Transfusion and intramuscular injection of untreated patients who reacted to the same pollens as the treated donor caused improvement in 16 to 20 patients following transfusion and in 60 to 90 patients following intramuscular injection. This report is in line with the trend of theory separating allergic and immunologic mechanisms (Rich and coworkers). These workers also note a lessening of the passive transfer reaction but with no apparent change in the skin test. The investigators postulate a "blocking mechanism" or substance not to be confused with the reagin. The reviewer wishes they had compared the "nonspecific" effect of blood injected or transfused from nonallergic individuals. Success has been claimed even for autoserous therapy by the Australian physicians, Maddox and Back.[59] A scientific approach, however, was entirely lacking. If Cooke and his coworkers verify their findings, they have made an important contribution. Perhaps combinations of allergen and serum from treated patients will be worth trying.

Mucous membranes have received more attention recently. Walzer, Sherman, and Feldman[60] have developed a modified Prausnitz-Küstner test. After anesthetizing the conjunctiva with 2 per cent butyn, they sensitized the site by subconjunctival injection of serum from individuals sensitive to ragweed and rabbit dander. The reaction to the specific allergens was clear-cut, but exhaustion was usual after the first response. Sensitivity persisted for five tests after an interval of thirty-four days in one case. Otorhinolaryngologists are increasingly interested in allergic phenomena. The review by Hansel[61] is most illuminating. Rowe[62] presented a discussion of nasal and bronchial allergy in childhood. He suggested that many conditions commonly accepted as infectious are on an allergic basis. In accord with the spirit of the times, he emphasizes general measures of nutrition (vitamin, calcium and phosphorus intake) as well as specific measures. He warns against nose and throat surgery as a solution of the asthma problem, though logically allowing it in certain studied cases, despite the report of Bullen previously discussed. The reviewer finds it difficult to believe that the period of September 15 to October 15 is that of the greatest incidence of allergic manifestations. Cohen[63] analyzed a series of 175 cases of nasal allergy and like Rowe found food the most important source of allergens. In contrast with Rowe, he has greater regard for the skin test as a guide for diet restriction. His

dietetic treatment seemed less empirical than that of Rowe. The overshadowing importance of foods might be challenged by those who find considerable incriminating evidence against inhalants. The skin test unquestionably has its failings, as have most of our biologic procedures. It seems unwise, however, to discontinue its use in favor of the elimination diet. Subjective symptoms are not above suspicion in the patient with psychic inclinations, and there is ample evidence which points to the danger of overemphasis of any one test or allergen so far discovered in allergy.

Considerable attention has been paid to iontophoresis or ionization[64, 65] of the nasal mucosa. Alexander's report[65] was preliminary and seemed to show encouragement, there being greater relief of symptoms in patients with negative skin tests. More recent discussion by the Association for the Study of Allergy, and elsewhere, does not seem encouraging. Indeed, evidence was presented which pointed to injury in the nature of fibrosis. Iontophoresis is such an intriguing name, and the popular interest in electric phenomena is so great that the writer marvels that the method had neither origin nor vogue in his state.

Air conditioning has become fairly well established in the armamentarium for respiratory allergy. An interesting paper by Hosmer[66] tells of obtaining relief, sometimes spectacular, in intractible or severe upper respiratory infections. The effects of air conditioning may be particularly beneficial in allergic conditions since it removes the irritant particles and furnishes ideal humidity and temperature. The air-filtering apparatus described by Criep and Green[67] is a far cry from the elaborate one of van Leeuwen.[68] Their apparatus has no effect on temperature and humidity but does remove pollen and dust particles efficiently. Symptomatic relief while in the air-filtered room was obtained in 61 patients with hay fever and asthma. The simplicity and the moderate cost of the machine are most commendable.

The past year has brought several reports dealing with pathology. This phase has seemed to be neglected because, except for the important experimental work, routine pathology has offered little explanation for functional disturbances. Kline and Young,[69] following Rossle's[70] theories, offer a discussion of reversible and irreversible allergic reactions. While adding to the confusion of nomenclature by the use of terms such as "hypergy," "hypo-ergy," "anergy," and "normergy," they have nevertheless endeavored to clarify the varying types of response. Fried,[71] working with rabbits, was able to produce an exudative inflammation of the lungs resembling lobar pneumonia. The rabbits were sensitized to horse serum and the shock injection was given intratracheally. Miller[72] and his associates report what may be the clinical parallel, "allergic bronchopneumonia." One is reminded of the splenic pneumonia or perifocal infiltration seen in tuberculosis. However, in the instance of pneumonia and respiratory infection seen in allergic children, the thesis is not as yet without controversy. The rôle of mucous plugs in atelectasis might explain some instances quite apart from allergy. Wilmer, Eiman and Miller[73] report the necropsy of a patient with essential bronchial asthma. Roentgen findings, antemortem and postmortem, are compared. The patient had had pollen asthma in his youth and a great emotional strain in adult life, which definitely accentuated his asthma. The presence of a renal stone had

prompted parathyroid investigation. Clinically, the patient presented a picture of profound emphysema in his terminal illness. The case illustrates the confusion in trying to recognize pathology related to functional disorders in the adult who has had superimposed and perhaps unrelated disease.

Michael and Rowe[74] report two postmortem studies of adults with chronic asthma. There was found in the lung smooth muscle hypertrophy, swelling of the mucosa (as was found in Wilmer's patient), mucus in the lumen, thickening and hyaline degeneration of the basement membrane and myositis of the bronchial muscle. One of their patients had an enlarged thymus and a small aorta and heart. Waldbott,[75] continuing his theme of anaphylactic rather than thymic death in infants, reports autopsies on two infants with acute asthma. Most of the findings of Michael and Rowe were absent, the main lesion being pulmonary edema probably from capillary permeability and secondary right ventricular dilatation. He emphasizes that these findings have been reported in the instances of "thymic death." The lymph gland enlargement suggests that perhaps some of the instances of mesenteric adenitis first described by Brennemann[76] may represent the pathology of allergy sensitivity. Some of the cases of mesenteric adenitis proved by exploratory laparotomy, which the reviewer has observed, have been in children with known food intolerance.

The literature of the past year contains many reports dealing with eczema. The pediatric department of the University of Minnesota has been studying blood fats in relation to various diseases. Hansen[77] contends, with regard to eczema, that there is a lowered amount of unsaturated fatty acids in the serum which may be raised by oral administration of unsaturated fat such as purified linseed oil. Cornbleet and Pace,[78] in a clinical application, reported improvement in a group of 87 patients treated with maize oil. They offered no chemical determinations to support the rationale of their treatment. Faber and Roberts,[79] in a small series of 15 eczematous infants and 16 controls, found that although the fatty acids tended to be low in the serum of eczematous infants, the difference was not sufficient to warrant Hansen's contention. They were not able to confirm the beneficial effects of corn oil. Taub and Zakon[80] are more devastating in their comments. They were unable to confirm Hansen's findings, and they called attention to the danger of indiscriminate use of linseed oil which may serve as the vehicle for cottonseed allergen. It would appear that the rôle of the unsaturated fatty acids (like hypochlorhydria previously discussed) is secondary and that sufficient studies to warrant a statistical analysis do not justify the interpretations given by some workers.

The use of soybean milk for feeding 205 infants was reported by Rittinger, Dembo, and Torrey.[81] They made careful observations on weight, growth, blood studies, and x-ray studies and found this vegetable milk an adequate food. The reviewer is forced to change his earlier view that this protein of vegetable origin is not a satisfactory "tissue builder." However, the inference which they make with regard to its use in eczema, based on the high ratio of unsaturated fatty acids, seems unwarranted in view of other reports. The cereal mixture of Tisdall, Drake, and Brown[82] was studied by Blatt and Schapiro.[83] Their observation of no allergic manifestation is of inter-

est, but without more data regarding the possible allergic susceptibility in the group the statement is of little value.

Hopkins and Kesten[84] report their observations and ideas on a group of 75 patients varying from one to twenty-seven years of age. The importance of family history and the rôles of certain foods are stressed. Silk and wool are considered inhalant ingestants rather than contact excitants. They reviewed much that is already familiar. Cobb[85] has published menus for the elimination of the common food offenders in childhood allergy. These are quite useful.

Hill and Sulzberger[86] present what might be called an orthodox American theory regarding the "evolution of atopic dermatitis." Infantile eczema and neurodermatitis in childhood and adult life are considered part of the same general mechanism. Admitting the hereditary background in about half the cases, they acknowledge placental transmission and acquisition of hypersensitivity. There was no discussion of the factors which might explain the frequency with which skin manifestations are limited to infancy in some and persist throughout life in others. Schiff,[87] in discussing neurodermatitis of childhood, gives a much more empirical program for treatment than that which the allergic theory indicates. Advising such foods as radishes and cucumbers in the raw fruit and vegetable diet for three-year-olds is rather surprising.

Ratner[88] has reiterated his thesis of acquisition and placental transmission. In a general discussion of milk allergy, he advises the use of heat to alter the lactalbumin and globulin fractions which are the chief offending fractions. This author[89] has also reported in more detail the results of animal experiments which show that the (noncasein) whey fraction loses some antigenicity on evaporating or heating. Concerning the sugars used for infant feeding, his experiments showed that malt extracts were often offenders because of the barley but that corn syrup and pure dextrimaltose were free from allergic implication. Tallerman,[90] using the passive transfer technic of Prausnitz-Küstner, found evidence of circulating reagin in the blood of infants with gastroenteritis. He suggests that clinical toxemia may be related to an allergic reaction. This was precisely the thesis of the work of Schloss and Anderson[91] several years ago. Walzer and Walzer,[92] also using the passive transfer method, obtained positive reactions after oral administration of the antigen. This, of course, is further evidence of the absorption of unaltered proteins.

The views of Worringer[93] on the problem of eczema are more acceptable than those of Schiff.[94] Worringer is primarily interested in eczema and allergy of infants and has discussed various theories of origin, postnatal acquisition, intrauterine or placental transmission, and hereditary factors. The same views are again expressed in his observations regarding infantile eczema.[95] He rejects the theory of passive transfer in utero and feels that Ratner's placental transmission does not represent the usual mode of sensitization. He strongly supports the hereditary factor inherent in both male or female germ cells and supports his contentions with convincing reasoning. The reviewer is in agreement with his refutation of sensitization through maternal milk.

The acquisition of sensitivity (or induction of latent capacity) is attracting considerable attention. Goldman and Pfosi[96] studied lacquer

dermatitis. The authors tested 61 patients by a patch test suggested to determine the extent of similarity between natural lacquer (Japanese) and *Rhus toxicodendron*. There were 29 positives to the natural lacquer, two to the artificial lacquer. There were 12 positive reactors in the control group of 98, which included six individuals with "neurodermatitis." No specific note is given regarding the response in the patients with neurodermatitis, nor is there any discussion of the effect of age. The group included patients as young as two years, at which age the skin is notoriously susceptible to nonspecific irritation, a fact which makes the patch test of doubtful interpretation. The authors stress the rôle of industrial exposure.

Colmes, Guild, and Rackemann,[97] in studying the influence of occupation on sensitization, reported a rather high percentage of positive wheat tests in thirty-two bakers. Only one verified instance of clinical sensitivity could be found, but the authors emphasized acquisition rather than hereditary predisposition as etiologic. Duke's report[98] on wheat millers' asthma, with a study of the morphology of the wheat germ, suggests that an inhalant from the "bearded" portion of the outer cells may be responsible. He found that wheat dust extracts gave positive reactions where the ordinary fractions failed. Passive transfer verified the presence of reagins for the wheat hair factor as did also the microscopic study of dust collected in a fashion similar to that used in pollen surveys. Comparison with tests of house dust extract was not offered.

The report of Vaughan and Fowlkes[99] on allergic reactions associated with cohabitation might be mentioned in reference to acquisition and the effect of exposure though it is not occupational. Details may be omitted since it is the writer's experience with his medical students that this is one report which will not be overlooked. The same may be said of Cooper's[100] report on semen allergy in children. Both reports are unusual but authentic.

Hypersensitiveness to insulin was studied by Sammis.[101] Reagins were found for both animal and synthetic insulin. The previous discussion of Tuft[102] is perhaps more comprehensive. The report last year by Bayer[103] on desensitization in insulin allergy is of value.

Jiminez-Diaz and Cuenca[104] report instances of unusual antigens responsible for asthma. Linseed insect protein, chicory, and tobacco are mentioned by these Spanish investigators. Chobot[105] discusses the significance of skin tests to tobacco in allergic children. He tested 52 patients; 6 gave marked reactions, 2 moderate, and 11 mild reactions. The reviewer has found that interpretation of the tobacco reaction in young children is very difficult. Babcock's report[106] on catgut allergy suggests an interpretation of some of the peculiar reactions in sutures heretofore enigmatic. No evidence was found by Stevens[107] incriminating cottonseed allergy from gin.

Cutaneous allergy following amidopyrine ingestion was reported by Taussig.[108] Skin tests were negative, but the clinical response of angioneurotic edema was definite. There had been an interval of time between the first ingestion of the drug and that which precipitated this response in the patient who was known to be allergic. New also in the lore of potential allergens is the suggestion of Fonde and Fonde.[109] They suspect the "honeydew" of the live oak trees of the South as a cause of hay fever. The material is the product of small insects infecting the oak leaves.

Blumstein[110] found 19 positive skin reactors to buckwheat in a group of reactors, mostly from inhalation (bakers). He found no evidence to incriminate buckwheat in relation to photosensitization.

At the University of Michigan, Sheldon and Randolph[111] found 127 of the student patients with migraine. There was a family history of allergy in 81.6 per cent of this group, mostly from the maternal side. An elimination diet was effective in about 38 per cent of the cases. Vaughan[112] is also of the opinion that food sensitivity is a factor in migraine. He found about 70 per cent of the instances of migraine associated with allergy in the absence of organic conditions, though it is not clear how completely these organic conditions are ruled out. Supervision, cooperation, the use of skin tests, food diary, and the leucopenic index are responsible for his rather high percentage of success. The reviewer still feels that migraine is pretty much of a riddle and that many other conditions besides allergy must be considered.

Psoriasis is the most recent disease to be suspected as an allergic manifestation. Adamson[113] tested the skin and injected the extract of psoriatic scales. The latter procedure is suggestive of a possible nonspecific effect as in autoserous therapy. The conditions in the newborn which Mayerhofer[114] considers allergic are toxic erythema, pylorospasm, melena, and hydrocele. The reviewer is most skeptical but admits the report should stimulate investigations in this newer field.

On the subject of therapeutics, the readers may find the Cook County Hospital Therapeutics of value. While dealing chiefly with contact dermatitis, the authors, Fantus and Cornbleet,[115] apply accepted allergic methods for diagnosis and treatment. Thiberge[116] compared the effects of histamine and typhoid protein in control of asthma and hay fever. He found both useful as nonspecific agents but felt typhoid split protein safer. The new vaporizer[117] for epinephrine inhalation has proved of definite value in the treatment of severe asthmatic attacks. Dzsinich[118] treated 15 asthmatic patients with graded histamine injections. He feels that the use of this agent is justified even though he did have some failures. The reviewer would call attention to the fact that the present enthusiasm for histamine probably dates from Lewis'[119] study of urticaria. Yet Lewis was most careful to use the term histamine-like in reference to the toxin from cell injury. The drug is not without danger even in minute amounts and should not be advocated for indiscriminate use.

The study of allergy is still in its infancy. While empirical treatment should have a trial, it is not a substitute for detailed sleuthing and study of individual patients. This naturally makes it difficult to accumulate careful studies of sufficient magnitude to warrant statistical analysis.

The Association for the Study of Allergy has started a program of certification for clinics dealing with the allergic problem. The reviewer has mixed feelings about such standardizations. Starting with the American Medical Association and the College of Surgeons, there has been a rush to specialty organizations and programs for certification. In a subject as new as allergy is there not still room for nonconformity? Is there not danger in setting standards for technic that are controversial or in cramping initiative and individual observations? Perhaps it will be found a difficult but "noble experiment."

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American Academy of Pediatrics

Proceedings

FIFTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

NEW YORK CITY, JUNE 7, 1935

Round Table Discussion on Encephalitis

Chairman: Dr. Josephine B. Neal, New York, N. Y. Assistant: Dr. Thomas M. Rivers, New York, N. Y.

The meeting was called to order at 2:30 P.M., at the Hotel Waldorf-Astoria, by the chairman, Dr. Josephine B. Neal.

CHAIRMAN NEAL.—As the years have passed since encephalitis has been more or less prevalent, the new problems that have arisen have far outstripped any advances that have been made in the solution of them.

It, of course, is quite impossible to cover the subject of encephalitis at all adequately in a short discussion. There is one point that I would like to emphasize—however, we so often hear the term "von Economo's encephalitis" as if this were a separate and distinct entity that should be recognized clinically. People who use this expression are, I think, quite unfamiliar with what von Economo himself wrote. In describing the small group of cases that he studied and worked up so admirably in Vienna, he took occasion to emphasize the wide variation in the clinical symptoms, and he stated that the only one consistent finding was the lesions in the basal ganglia.

In my part of the discussion I shall not go into the pathology of encephalitis, but I remember hearing Dr. Tilney say that the reason lesions in the basal ganglia were so much emphasized was mainly that pathologists had not searched sufficiently in other parts of the brain, that in encephalitis the lesions were, as a matter of fact, widespread.

Another point worth considering at this meeting particularly is that encephalitis occurs more frequently in children than is generally known. Encephalitis attacks all ages, from children only a few days old to adults in the seventies and eighties. The acute stage of encephalitis very often passes undiagnosed.

The clinical picture in children is very widely varied, and in these later years since encephalitis has been prevalent, we have seen a relatively large number of cases of encephalitis following measles, chickenpox, whooping cough, occasionally scarlet fever. The meningoencephalitis following mumps has always been more or less prevalent, even before epidemic encephalitis became prevalent. This seems to be a rather clear-cut clinical picture of meningoencephalitis, and it may precede the development of the parotitis.

In these other forms of encephalitis, including that following vaccination, of which fortunately we have had very little in this country, the clinical picture varies very greatly, and these patients also in certain instances go on to the chronic stage of

the disease, in which they show varied manifestations. When encephalitis first became prevalent, we thought that the chronic stage was a sequela of the acute stage, and, if it were to develop at all, we expected it to develop within a matter of months or at the most a year. As time has gone on, however, we find that patients may be restored apparently to complete health and may remain so up to ten or more before the chronic stage develops. Of course, in the majority of cases it does make its appearance within the first five years.

Encephalitis is the most terrible disease that I know, and its effects in children are even more devastating than in adults. In children encephalitis in any form is frequently followed by mental deterioration and moral degeneration, with or without definite neurologic changes. Of course, a certain number of them may go on into the parkinsonian stage at a later date, and we do see parkinsonism developing occasionally in fairly young children, but on the whole the mental and moral changes are much more pronounced than the actual physical changes. In adults, on the other hand, there are rarely changes in the mentality or in morals.

The question of encephalitis has been still further thrown into confusion by the development of the St. Louis epidemic. Up to that time, many of us had hoped that a single etiologic agent might be responsible for these cases. The etiology of encephalitis following vaccination, measles, and other acute infections was an entirely open question. But with the development of the St. Louis epidemic and the isolation of a new virus, we now recognize the fact that there must be more than one etiologic agent. How many etiologic agents there are time alone can tell.

As time has gone on, the clinical picture of encephalitis has perhaps changed more or less, that is, the preponderance of the symptoms have changed, and whether this is due to coming in of the new viruses or to other factors, I do not know. Dr. Rivers can answer that much more adequately.

The diagnosis of encephalitis must be made by ruling out as many diseases as possible. Of course, meningitis, particularly tuberculous meningitis, may be ruled out by lumbar puncture. A Wassermann test must be made on all spinal fluids in cases of suspected encephalitis. In encephalitis there is ordinarily a change in the spinal fluid, an increase in cells, which varies very greatly, usually a preponderance of mononuclears, occasionally polymorphonuclears, often an increase in protein and a normal or high spinal fluid sugar content. There may be an increase in cells without much change in the protein, or the increase in the protein may be much greater than the relative increase in number of cells. Occasionally we see cases, undoubtedly encephalitis, in which the spinal fluid findings are within normal limits.

If patients suffering from encephalitis have increased pressure of the spinal fluid, lumbar punctures should be performed as indicated until the pressure becomes normal. The intravenous injection of hypertonic glucose aids in reducing the increased intracranial pressure. Hypertonic glucose also serves as a cardiac stimulant and is of general benefit to the patient.

On the premise that a virus closely allied to the herpes virus may be the cause of certain forms of encephalitis, we have been using a vaccine in treating cases both in the acute and in the chronic stages. A certain percentage of the patients treated in the chronic stage have shown some improvement over a period of years. Whether improvement is due to the vaccine or not, I have no firm conviction. We have treated a fairly large number of patients in the acute stage with the hope that the development of the chronic stage might be averted. So far, and this is up to a period of five years, none of the patients treated in the acute stage has gone into the chronic stage of the disease.

It is only by following these cases over many more years that we can be sure whether or not the vaccine was of any value in building up a sufficient immunity to avert development of the chronic stage.

One could talk about encephalitis indefinitely. At this point I will ask Dr. Rivers to go on with the discussion.

DR. THOMAS M. RIVERS (NEW YORK).—Encephalitis means nothing more than an inflammation of the brain, and it can be caused in a number of ways, for instance, by protozoan parasites as in African sleeping sickness or as in toxoplasma infections of rodents, by fungi, by bacteria as in encephalitis complicating bacterial endocarditis, by spirochetes as in paresis, or by rickettsia as in typhus fever. In addition to these infectious agents which produce an inflammation of the brain, there is another group of agents known as the viruses or filtrable viruses which produce encephalitis; and, more or less by consent, when one says encephalitis, one usually thinks of inflammation of the brain caused by the viruses. That is what I am going to talk about this afternoon. That is what Dr. Neal has been talking about already.

Encephalitis is certainly not a clinical entity. Some day we will be able to divide the large group of cases of encephalitis into smaller groups and assign to each one its real etiologic agent. Until we can do that, the whole field of encephalitis is going to be in a very much confused state.

Our attention was first called to encephalitis forcibly during and after the war by the so-called von Economo's encephalitis or lethargic encephalitis or epidemic encephalitis. All of those names are very unfortunate because any encephalitis occurring epidemically can be epidemic encephalitis; lethargic encephalitis, von Economo's disease, may be anything but lethargic because the patient may be highly agitated. Thus the names that we have used to designate the cases of encephalitis occurring during and after the war, that is von Economo's lethargic encephalitis and epidemic encephalitis, are certainly inadequate and confusing.

We will discuss that group of cases first. I will hazard the statement that the majority of the cases occurring pandemically were caused by a single etiologic agent even though they were very different clinically. As to whether any individual case that was seen at that time represented epidemic encephalitis, I don't think it would be possible for one to say. As to the etiology of this group of cases, we are still ignorant. Of course, a number of people contend that herpes virus, the virus which causes fever blisters, is responsible. Levaditi in France, is particularly in favor of such an idea. Dr. Gay and others in this country favor it also. Personally, I am rather opposed to the idea, and I agree with Dr. Neal, who has just said that the etiology is decidedly still an open question.

Now we come to another group of cases, those that occurred in St. Louis in 1933. As a whole, that group of cases was clinically different from the major portion of the cases which occurred during and after the war. In the first place, practically all of the patients went back to work within three weeks. In another respect, the cases in St. Louis were different from the ones that occurred after the war: the age incidence was distinctly higher in the St. Louis group than in the other type. Furthermore, a number of people were able to recover a virus from the cases in St. Louis. As a matter of fact, it was rather easy to recover a virus from those cases. The virus can be transmitted to monkeys fairly well and very well to mice. If the cases that occurred after the war had had a virus similar to the one in St. Louis, I am sure that a large number of people would have recovered it, because excellent men attempted to transmit the disease to lower animals without success. Thus, the cause of the St. Louis encephalitis is definitely known. It is a very small virus, one of the smallest. Its diameter is about 15 to 20 mμ. It won't multiply on ordinary media and can be carried only in some susceptible host.

Serum from the majority of the individuals who have recovered from the St. Louis type of encephalitis neutralizes the virus that has been isolated. On the other hand, serum from individuals who had von Economo's or pandemic, epidemic, or lethargic encephalitis will not neutralize the St. Louis virus.

Thus we have a certain amount of clinical evidence that the so-called von Economo's disease and the St. Louis disease are different, but we have excellent experimental evidence to show that they are different.

Not only did the patients who recovered from the St. Louis type of encephalitis have neutralizing serums for this virus but serums from many of the contacts in the St. Louis area who did not have any visible disease also possessed neutralizing properties, whereas serums from normal people in France or normal people here in New York City do not neutralize the virus.

Another question arises as to whether the St. Louis type of encephalitis has occurred anywhere else in the world, or whether it occurred before 1933. Yes it occurred in Paris, Ill., in 1932. Dr. Webster has been able to get serums from individuals who recovered from a small epidemic of encephalitis in Paris, Ill., and he has found that all of them neutralize the St. Louis virus. In 1933, we had two cases of the St. Louis encephalitis here in New York. Not only did the St. Louis virus occur in this country before 1933, but it has occurred since, as Dr. Webster is now able to show that a certain number of cases occurred in various places during the summer of 1934.

So it looks as though we may have a definite encephalitis caused by a virus that we can isolate and recognize serologically. Now, is there an encephalitis like the St. Louis encephalitis occurring anywhere else in the world except in the United States? There is in Japan, a type of encephalitis called summer encephalitis. It occurs mostly in old people or in people beyond middle life. It occurs in the summertime and has a high mortality. Epidemologically, clinically, and pathologically the summer encephalitis in Japan looks very much like the summer encephalitis in St. Louis in 1933, but serums from the people who have recovered from the summer encephalitis in Japan do not neutralize the virus which caused the epidemic in St. Louis.

The disease in St. Louis and the disease in Japan are alike clinically, epidemologically, and pathologically; yet they are caused by viruses which are not serologically similar. That may seem very peculiar, but it is not very peculiar when one considers encephalitis in lower animals. For instance, we have here in the United States equine encephalomyelitis. It attacks horses both in the western and in the eastern part of the continent. The virus which causes the disease in the East—the disease is very much alike in the two localities—is different from the virus which causes the disease in the West, that is, they are different immunologically. So it is not peculiar that we have in St. Louis an encephalitis like that in Japan and still have them caused by viruses that are immunologically different.

Now we come to the encephalitis which follows measles, chickenpox, vaccination against smallpox, vaccination against rabies, etc. Clinically it is like any other encephalitis. It has bizarre manifestations in the individual case, such that in the individual case it is almost impossible to be sure of what one is dealing with except that it is postinfection encephalitis.

Such cases for the most part are different pathologically from the types of encephalitis that I have already mentioned. In the majority of cases of postmeasles, postvaccinal, postvaricella, postrabic vaccination encephalitis, perivascular demyelination occurs. That does not mean that every patient who has encephalitis following measles is going to have perivascular demyelination because a certain number of such patients have died and at autopsy have failed to show perivascular demyelination. The group of cases of encephalitis showing perivascular demyelination is distinctly different from the other cases of encephalitis that Dr. Neal and I have been talking about.

A number of people have suggested that the vaccine virus or rabic or varicella virus is responsible for this kind of encephalitis. My own opinion is this: No known virus acting directly on the central nervous system produces a perivascular

demyelinating type of encephalitis. Therefore, it would be very unlikely for the viruses of measles, rabies, or vaccinia to produce a perivascular demyelination as the result of their direct action upon nerve tissue. I do not know whether you get that or not; I think it is a very important fact. Vaccine virus put into the brain of a large number of animals produces encephalitis or meningitis, but it does not produce a perivascular demyelination. Rabic virus put into the brain of an animal never produces perivascular demyelination. Yet the encephalitis which follows vaccination against smallpox and encephalitis which follows vaccination against rabies is characterized in most instances by a perivascular demyelination. Now, it would be a very peculiar virus that would attack the myelin and not attack the cells. If our conception of viruses is correct, that is, if they are intracellular parasites, then the neurons, the nerve cells, should be damaged, but in the typical postvaccinal cases, there is little or no damage of the nerve cells. The main picture is a loss of myelin. So, without knowing what causes the demyelinating encephalitis following measles, vaccination, etc., I am postulating that it is very unlikely to be a virus.

Is there any evidence in regard to the mechanism of demyelination in these cases? A number of people think that the perivascular demyelination that follows vaccination against rabies is due to the brain substance injected during the process of vaccination. A certain amount of experimentation has been done. If one repeatedly injects sheep brain into rabbits, about 30 per cent of the animals become paralyzed. Unfortunately, no pathologic changes in the central nervous system have been found to account for this paralysis. We had an idea that maybe demyelination is not possible in the rabbit. The rabbit would become paralyzed, but demyelination could not be produced. We transferred our work to the monkey. We have been repeatedly injecting monkeys with normal rabbit brain, and for two years in succession we have been able to paralyze monkeys. With repeated intramuscular injections of normal rabbit brain, we paralyzed two of eight monkeys the first year and seven of eight monkeys the second year. When we killed the monkeys and examined them, we found perivascular demyelination. Unfortunately, the picture is not identical with that seen in the human being. There are a number of things in the monkeys so different from what we see in human beings that I don't know whether we have solved the question of perivascular demyelination or not. I am inclined to think we have not, but we do know that we can paralyze monkeys and get perivascular demyelination by repeatedly injecting into them normal rabbit brain.

We have not been able to transmit this demyelinating disease to other monkeys in series. We cannot transmit it to rabbits, guinea pigs, or mice. We believe, nevertheless, that it is a result of the repeated injections of normal brain.

I think for the time being that the etiology of the perivascular demyelinating type of encephalitis that following various infectious diseases has to be considered an open question. I do have very strong convictions, though, that it is probably not caused by the direct action of a virus.

The meningoencephalitis of mumps is probably caused by the virus of mumps. I do not think that we need to go any further into that question. The experimental proof has not been brought yet that that is the case, but I think that it will be brought now that Dr. Goodpasture has been able to transmit mumps to monkeys.

We have talked in a general way about a large group of cases in St. Louis and about a large group of cases which occurred during and after the war, and about a large group of cases which occurs after certain acute infections. What we have said in regard to these groups as a whole is probably true, but I am quite convinced that there are many other smaller groups of cases of encephalitis the etiologic agents of which have not been found which are being classified either with the St. Louis group or with von Economo's or epidemic group. I think the best proof I can give you of this is that just recently we have been able to isolate a new virus from two

human beings with involvement of the central nervous system. Two adults came under our observation almost simultaneously, one in Princeton and one in New York. The clinical picture in these two cases was almost identical. The individuals were sick with something that looked like influenza for a few days and then went back to work feeling bad. Then after they had been back at work for a few days, they were taken ill with terrific headaches. The headaches were so bad the patients could not sleep and various drugs gave no relief. One of the patients was seen by a physician here in New York, and a tentative diagnosis of epidemic meningitis was made. The spinal fluid cell count was 1,700 per cubic millimeter and practically all of the cells were lymphocytes. Quite obviously it was not meningococcic encephalitis, and a diagnosis of encephalitis was made. We put some spinal fluid into animals and were able to recover a virus without any difficulty.

We saw the other patient in Princeton a week after the onset of his headache. He had a slightly stiff neck. The cell count in the spinal fluid was approximately 750 per cubic millimeter, and without any difficulty at all we also obtained a virus from that spinal fluid. The virus from that spinal fluid turned out to be identical with the virus from the spinal fluid of the first patient. As we studied the virus, we recognized that it was similar to the virus described in 1934 by Dr. Armstrong and Dr. Lillie, in Washington, and similar to the one isolated from normal-looking mice by Dr. Traub in Princeton. Between us we have been able to show that the virus from the patient here in New York, the virus of Dr. Armstrong and Dr. Lillie in Washington, and the virus of Dr. Traub in Princeton are identical.

Just how important this new virus is in regard to human disease we do not know, but there has been described in human beings what is known as acute aseptic meningitis, and there are some indications that a few of these cases are caused by this new virus.

I have just told you about these two cases in order to show that there certainly are other viruses active in the central nervous system of man in addition to those which produce epidemic encephalitis or von Economo's disease and the St. Louis type of encephalitis. As to how many viruses we are going to discover that attack the central nervous system of man and how many viruses are going to be found responsible for the condition we speak of rather loosely as encephalitis, there is no way of knowing at the moment.

Eventually diagnoses in this field are going to be made on the basis of etiology. I do not see how it is going to be possible to place the different kinds of encephalitis in the classifications clinically or pathologically because the same virus can produce different clinical and pathologic pictures in the central nervous system or different viruses can produce the same clinical and pathologic pictures.

Let us suppose you have a case of meningitis, you can make a diagnosis of meningitis, but to say what kind, you must determine the bacteria responsible. You must find out whether it is caused by a pneumococcus, streptococcus, staphylococcus, etc. The same applies to encephalitis. In the individual case, without the use of the laboratory, you cannot tell accurately what kind of encephalitis you are working with. Unfortunately, at the moment, we can only give a laboratory diagnosis on one or two types of encephalitis, the St. Louis type and possibly the new type just recently discovered. There is coming a time, though, when laboratory workers will be able to give the clinician an accurate diagnosis.

CHAIRMAN NEAL.—I would like to make two comments in regard to the question of encephalitis following measles and vaccination. One point is that, while there is no doubt demyelination may be produced in monkeys by the injection of rabbit's brain and therefore that might account for the pathologic picture in the occasional cases of encephalomyelitis that we see following the antirabic treatment, it

would not account for the demyelination in the cases following measles or following vaccine in which no brain substance had been injected. There would have to be some other factor which Dr. Rivers, of course, indicated.

Another is that the clinicians who have been working for many years quite unanimously agree that before epidemic encephalitis made its appearance in this country we did not see, except with very rare exceptions, cases of encephalitis following measles or vaccination. The clinical picture is arresting enough so that had it occurred we hardly could have missed it. I am not trying to give any explanation for these cases following measles, but I do entirely agree with Dr. Rivers when he says that he does not think the virus of measles, or of vaccinia, or of chickenpox is responsible for these cases of encephalitis. What it can be, whether it is an interreaction of two viruses or just what it is, I am sure I don't know.

We will now leave the questions open for discussion.

DISCUSSION

DR. RIVERS.—May I reply to one comment? I did not want to get too deep into this question of demyelination because we are working on it, and I do not want to lead you to believe that we have settled it. You said with regard to measles and vaccinia, etc., no brain material had been injected. We have been going on the assumption that some tissue in the body has been damaged or altered sufficiently by, say, the virus of measles or the virus of vaccinia, or other viruses, that it becomes antigenic for the hemologous host. We took rabbit brain out sterilely, ground it up, and allowed it to autolyze at room temperature. Then after it had autolyzed at room temperature, we repeatedly injected that autolyzed brain tissue into rabbits. That autolyzed brain tissue paralyzed rabbits. We could not find any demyelination in the rabbits, but 30 per cent of the rabbits were paralyzed. Not only were they paralyzed, but they developed antibodies against rabbit brain. Fresh rabbit brain taken out and immediately injected into rabbits would not paralyze rabbits and would not produce any antibodies.

It is a rather interesting fact that most of the diseases that give rise to perivascular myelination are the ones that attack the skin, e.g., smallpox, chickenpox, measles, vaccinia. The skin is involved, and the skin comes from the same source as does the brain. We have been thinking that it is barely possible that the viruses alter the skin in such a manner that the altered skin will then become antigenic for the homologous host and that, inasmuch as the brain and the skin come from the same source, the perivascular myelination might be accounted for in this manner.

DR. NEAL.—Why did not our skins react that way in 1910 and 1911?

DR. RIVERS.—Of course, there is the host factor. Why is it that one year I only got two paralyzed monkeys out of eight and seven out of eight the next year? There must be a host factor. For some reason or other, genetic or environmental, the human being, the host, is being changed so that now certain things are occurring more frequently than they did previously.

DR. CHARLES SCHOTT (CHICAGO, ILL.).—What was the difference in the type of cells and spinal fluid in the two cases that were recently observed in Princeton and New York from the ordinary type of encephalitis?

DR. RIVERS.—I do not know that they were particularly different. They were mainly lymphocytes.

DR. SCHOTT.—Why are cases of lymphocytic meningitis not encephalitis?

DR. RIVERS.—They may be, but Dr. Viets in Boston reported in the *Journal of the American Medical Association* several years ago that differentiation was made mainly on the clinical picture.

DR. SCHOTT.—Recently the son of one of our colleagues had what was called a lymphocytic meningitis. There was an epidemic of parotitis in the neighborhood at the time although he did not have mumps.

DR. RIVERS.—I have seen here in New York this winter a number of cases with very high cell counts. One of the internes at Columbia had measles and then developed postmeasles encephalitis. He had a cell count of a thousand, which is high for a postmeasles encephalitis. Then we had a patient at the New York Hospital with a cell count of 1,200. I have had many patients with cell counts above 500; in ordinary encephalitis one does not find such high cell counts. Is not that true, as a rule?

DR. NEAL.—You will occasionally see high cell counts in encephalitis just as you will occasionally in poliomyelitis, but it is exceptional.

DR. RIVERS.—I believe Dr. Neal can answer this question better than I can, but I will state what I think about these cases of so-called acute aseptic meningitis. They have, as a rule, high cell counts; the clinical picture is more of a meningitis than encephalitis; and recovery is slow yet complete so far as I know. The true cases have not the sequelae that follow epidemic encephalitis.

DR. SCHOTT.—In the literature there is evidence that there were cases of encephalitis following the epidemic of influenza in 1892 and 1893. Is that correct?

DR. NEAL.—I think there probably was more or less encephalitis at that time. I suppose encephalitis can follow influenza just as it can follow other acute infections. In fact, when we first began seeing encephalitis here in the fall of 1918 and the spring of 1919, some of the patients had had influenza, and for a time we thought it was an encephalitis following influenza. Whether encephalitis following influenza has this same picture of demyelination, I do not know.

DR. RIVERS.—Greenfield has reported that encephalitis with demyelination occurs at times after influenza.

The important point to remember is that the type of encephalitis cannot be determined regularly by clinical means alone.

DR. SCHOTT.—Are the different complications due to a different virus, or is it individual to the patient?

DR. NEAL.—That I do not know. I am still following one of the first patients with encephalitis I saw here in New York. She has very little in the way of parkinsonism but is very distinctly of the hemiplegic type. When I first saw her, she looked as though she had an early case of tuberculous meningitis.

We have seen all sorts of sequelae or chronic forms following encephalitis in all of the different years. I am sure I do not know whether it is a different etiologic agent or whether it is a different localization of the virus or a different reaction on the part of the patient.

DR. RIVERS.—Of course, all symptoms that one observes in encephalitis are probably due to the direct or indirect action of a virus on some part of the brain. The location of the activity of the virus rather than the type of virus determines the character of the symptoms in the patient affected.

I can illustrate best by means of some cases of louping ill that I saw in human beings. Louping ill is a meningoencephalitis of sheep in Scotland and northern England. We brought the virus into this country to study its relation to the virus of poliomyelitis.

As a result of working with that virus, a certain number of laboratory people came down with encephalitis. It was rather interesting. One of the individuals had what looked like influenza, came back to work, and then developed a severe headache. He was seen by one of the leading physicians in New York, who made a diagnosis of tuberculous meningitis and gave a very bad prognosis. That patient immediately recovered and is still well.

Another individual had something similar to influenza, came back to work, then developed a severe headache, and went to bed. He was sent to my ward, and Dr. Tilney and I took care of him. We made a diagnosis of epidemic encephalitis, with typical diplopia, sleeplessness at nights, sighing respiration, and gave a very bad prognosis. That patient, immediately after we gave a bad prognosis, began to get well and is now perfectly healthy and has been healthy for two or three years since.

Another individual had a very severe headache and some trouble with the eyes. A diagnosis of influenza was made and the patient made a complete recovery.

Still another individual became sick, and a diagnosis was made of tuberculous meningitis. That individual promptly recovered and is still well.

Thus we have the same virus producing different clinical pictures. Without going into details, I can state that different viruses are capable of causing the similar clinical pictures.

DR. NEAL.—I wish doctors would not make a diagnosis of tuberculous meningitis until they have demonstrated the tubercle bacilli in the smear or until the spinal fluid sugar has become low with a normal blood sugar content.

DR. STERLING H. ASHMUN (DAYTON, OHIO).—I would like to ask your opinion regarding a patient whom I recently cared for, to see whether you think I may have been dealing with an encephalitis of one type and a meningitis of another type in the same individual. This baby was eighteen months old. The doctor had seen him three or four days before admission to the hospital and thought that he had influenza.

He was very stuporous, had a stiff neck and Kernig's sign to a moderate degree. There was no nystagmus or strabismus. There was a very marked bulging of the fontanel. A spinal puncture done immediately showed 300 cells. Since the spinal tap did not relieve the pressure, I made a puncture of the cisterna, which also failed to relieve the pressure as much as I thought it should. By the second day the right pupil had become very markedly dilated and the left was markedly contracted, which fact made me feel that there was a difference in the ventricles.

A ventriculogram, to my surprise, showed the dilated ventricle on the left and a slightly larger than normal ventricle on the right. The child's spinal fluid, in addition, showed a normal or slightly increased sugar. In the successive taps the number of cells dropped from 300 to 50. The child became suddenly worse on the fourth day and died on the fifth day. I was fortunate in securing a postmortem. I should have told you that the blood count was 20,000 white cells with 70 per cent polymorphonuclears. The tuberculin test was negative.

On postmortem examination, we found the brain was not much congested on the surface. The ventricles were as the picture had shown, and in the sylvian tract was a large tuberculous granuloma. Just under the cortex on the left was another tuberculous granuloma as large as my thumb, and in the postcerebral subcortical region was another. We also found a large tuberculous peritracheal lymph gland and the left suprarenal gland completely destroyed by tuberculosis.

Now, that picture as the baby came in was not one of tuberculous meningitis. It was more the picture of lethargic encephalitis following influenza. In the spinal fluid at no time were they able to find the tubercle bacilli, and there was no evidence of miliary tuberculosis in the brain. The temperature on admission was not high,

although it had been very high at the onset. The temperature rose, however, to 107° F. before death.

DR. NEAL.—I think that in the presence of tuberculomas one has the picture both in the spinal fluid and in the brain of multiple brain tumors and that the reaction of the tuberculomas and also the increased spinal fluid pressure would be sufficient to account for the child's symptoms resembling encephalitis. Of course, without a generalized tuberculous meningitis, there would be a normal spinal fluid sugar just as with a brain tumor, and probably it would be impossible to demonstrate the tubercle bacilli in the fluid.

DR. BRONSON CROTHERS (BOSTON).—The situation that Dr. Ashmun speaks of is rather rare, but it is absolutely characteristic, I should think, in certain cases of multiple tuberculous tumors. We have seen it in two cases in which the most searching examination of the spinal fluid was absolutely contradictory to tuberculosis from all points of view. In one case we knew it was tuberculosis, and in spite of that we got blocks in the spinal canal up toward the cerebellum and in the ventricle on one side. We practically demonstrated a diagram with the process, and yet we could not prove a single thing except the pressure relationship was all upset by block.

I would like to know about the criteria of recovery in children after any severe cerebral damage. We make many mistakes in prognosis in these children unless we wait a year from the time the processes come to a stop, and my guess is that a good many of the behavior disorders that follow encephalitis or other cerebral damage are due to a lack of recognition of the influence of the process on the mental equipment of the child. It is probable that we take recovery for granted when we get back to where we were before, without demanding that the child be put on the road to progress at a normal rate.

DR. NEAL.—Yes, I think that is true, and I think you are quite right in saying that a year and even much more must elapse before we can say anything very definite.

DR. JOSEPH STOKES, JR. (PHILADELPHIA).—Dr. Rivers, when the rabbits were injected with their own autolized tissue, how long did it take from final injection until the time that the paralysis developed?

DR. RIVERS.—The rabbits received as a rule about ten injections, two or three a week. They usually became paralyzed toward the end of the course of inoculations or shortly after their completion.

DR. STOKES.—In the case of the Princeton man, was that due to association with Traub's virus?

DR. RIVERS.—I do not know. We have no information in regard to that. All I can say is that our mice in New York, that is, the mice that we have in the Rockefeller Institute, are not infected with the new virus, and the individual here in New York who contracted the disease happened to be a painter who works at the Rockefeller Institute in New York. That virus is not in our stock animals. The virus is in the stock animals at Princeton. As to whether the man contracted it from some individual or from the mice down there, I do not know.

DR. STOKES.—Supposing monkey tissue is injected regularly as it is in vaccinating children against poliomyelitis, do you think that is at all dangerous in connection with the demyelination reaction in human beings?

DR. RIVERS.—In antirabic treatment, individuals get 2 c.c. every day for fourteen days. In other words, they get about 28 c.c. of a 4 or 5 per cent emulsion of rabbit brain injected subcutaneously. As I understand it, Dr. Brodie is giving one 5 c.c. dose of a 10 per cent emulsion of monkey brain. In other words, Brodie's

patients are getting one-third the amount of heterologous brain as do the people who are vaccinated against rabies. About one person in 4,000, according to the figures given by the report of the League of Nations, vaccinated against rabies comes down with postvaccination demyelinating encephalitis. If one person in 4,000 who gets 28 c.c. of a 5 per cent emulsion comes down and if things work mathematically, about one person in 12,000 or 15,000 might contract a demyelination encephalitis when vaccinated against poliomyelitis. That is purely a guess. Furthermore, in antirabic vaccination repeated doses are given while Brodie usually gives only one dose.

DR. R. M. POLLITZER (GREENVILLE, S. C.).—Would it be asking too much if one of you would give us what you consider the minimum basic diagnostic requirements?

DR. NEAL.—I will say frankly that I do not know. I do not know any way to differentiate absolutely a nonparalytic type of poliomyelitis from a meningeal type of encephalitis.

There are two signs that I place more or less reliance on if they happen to be present. One is that in encephalitis there is quite often an absence of the abdominal reflexes. I know they found this in St. Louis. In poliomyelitis I expect the abdominal reflexes to be normal unless there is a paralysis of underlying muscles which does not occur in a nonparalytic case. The pupillary reflexes are usually normal in poliomyelitis unless there is an extremely increased intracranial pressure which usually is not present, whereas quite frequently in encephalitis there is some disturbance of the pupillary reflexes, either their reaction to light or to accommodation or to both. Thus, I think we can make a diagnosis in which we will be correct in a fairly large percentage of cases of meningeal type of encephalitis with those two symptoms and particularly with some changes in the spinal fluid.

Then there are patients who are more or less monosymptomatic—I do not know that this occurs in children so often, I have not seen it at any rate—who will have just diplopia for a while and be able to go about their work although more or less annoyed with disturbance of vision. Some time later a chronic stage develops. Excessive drowsiness or insomnia or reversal of the sleep rhythm or mental disturbances strangely suggest encephalitis. In poliomyelitis it is very unusual to see any mental disturbance otherwise than somnolence. Delirium of one type or another is fairly common in encephalitis. Cranial nerve palsies occur in both conditions. I know of no way of differentiating the occasional rare case of the encephalitic type of poliomyelitis from an encephalitis, nor the ataxic type of poliomyelitis from an encephalitis with ataxic symptoms.

DR. BERMAN S. DUNHAM (TOLEDO, O).—How long would the serum be positive?

DR. RIVERS.—In the St. Louis type of encephalitis, the antibodies usually develop rather rapidly, that is, within two or three weeks after the onset of the disease.

DR. DUNHAM.—When does it disappear?

DR. RIVERS.—So far as I know most of these patients who develop positive blood signs still retain them. That is true of a number of virus diseases; once you have had a virus disease, your blood possesses antibodies against it many years afterward, sometimes throughout life. One attack of yellow fever, for instance, will supply you with antibodies in the blood the rest of your life even though you live fifty to seventy years after that attack. That is not true of all virus diseases, however. In poliomyelitis once a person gets antibodies he usually keeps them.

The patients in St. Louis who developed antiviral antibodies seem to retain them. It is rather interesting, however, that some of the patients in St. Louis who had what appeared to be the St. Louis type of encephalitis have never developed anti-

bodies against the St. Louis virus. Now, whether these individuals had something different from the St. Louis type of encephalitis or whether they were people who were incapable of producing antibodies and may have a second attack of the St. Louis type, I do not know.

DR. ALTON GOLDBLOOM (MONTREAL, QUE.).—I should like to discuss a rather interesting group of cases that we have seen in Canada. Both during and out of poliomyelitis seasons children will be brought into a hospital with symptoms resembling poliomyelitis, the only difference being that in most of these cases the spinal fluid findings were entirely negative. In the course of two or three weeks, the paralyses disappeared in spite of the fact that they were complete when they occurred.

Several English writers have referred to this condition as infectious polyneuritis. I should like to ask if this condition might be a virus disease. I have not been quite in favor of accepting this as a polyneuritis because in polyneuritis one would not have central nervous system symptoms such as drowsiness and headache, vomiting, especially the inability to sit up or the inability to bend forward, and Vipond's sign, exactly as one sees in poliomyelitis, but with negative spinal fluid findings and complete and rapid disappearance of the signs.

DR. NEAL.—We do see an occasional case that seems to be poliomyelitis either with or without changes in the spinal fluids, in which the paralysis clears up very quickly. I think most of us have assumed that was because there was very little damage to the cells, just edema, and with the disappearance of edema there was the disappearance of the symptoms. I have seen cases like that but rather rarely. I do not know what I would think if I saw any number of them.

DR. R. C. BOND (WHEELING, W. VA.).—During the last three weeks I have been seeing postmeasles encephalitis.

Two patients were sent into the hospital: one a child, eight months old, in convulsions, and the other with headache, drowsiness, vomiting of sudden onset.

This eight-month-old baby continued in convulsions. Lumbar puncture showed 87 lymphocytes, a blood sugar of 120 mg., a spinal fluid sugar of 35, a negative tuberculin test, and a negative roentgenogram of the chest for miliary tuberculosis. After the convulsions diminished, there was a definite spasticity of the right arm that never did relax.

I thought the child had a case of tuberculous meningitis with the low spinal fluid sugar. Two days later the spinal fluid sugar was down to 30 mg. Later, however, he recovered, apparently, but the involvement of the arm remained. I still think he had tuberculous infection and that we shall see him later.

The other chap was four years old. He was drowsy, listless, and had a stiff neck. He did not respond to questions. The spinal fluid showed 51 mg. of sugar and 10 lymphocytes. The next day we demonstrated a diplopia, a bilateral fourth nerve paralysis, and pupils that failed to react to light. Since the history showed the child had just recovered from measles, I made a diagnosis of measles encephalitis.

The child stayed stuporous and very drowsy for three or four days, but after glucose and repeated lumbar puncture the child made an uneventful recovery and the eye muscles became normal.

A third child was seen on the ninth day of measles. He had been drowsy from Sunday until Thursday, taking no food or water. He could not be aroused. He was stiff, just like a mummy, with cogwheel resistance in both arms and legs. The muscles of his face were immobile. Lumbar puncture revealed 18 lymphocytes and a normal sugar content. He could not talk or swallow.

The neurologic examination revealed a stiff neck, a paralysis of the tenth, eleventh, and twelfth cranial nerves. We could not test smell or hearing. His reflexes were a little hyperactive. He remained very stuporous for about seven days.

On the eighth day he said, "Damn it." After that he started to respond by "uh-huh" if asked a question. At the end of the second week he began to yawn, and he sneezed a few times. He said a few words.

In the last few days he has moved his left leg, and has some grip in the left hand. His face is still masklike, but he will cry a little now. He has become less lethargic and more restless, and sedatives have been used. The cell count in the spinal fluid has never gone above 18. The spinal fluid sugar has been normal.

I wonder about the prognosis of this case and if there is anything more to do than I am doing. I am giving glucose intravenously frequently and am making lumbar punctures every day or every other day. He is getting food high in calories by nasal feedings and mild saline cathartics.

Another question is this: Is the severity of sequelae or the chronic state different from that of epidemic encephalitis and is the prognosis just as unfavorable as in epidemic encephalitis? Also I should like to know the relation of the cell count to the severity of the attack.

I had a patient with mumps encephalitis with over 800 cells and two patients with measles encephalitis with over 200 cells, all of whom went on to normal recovery and so far have had no sequelae. Does the lack of cellular response make the prognosis more unfavorable?

DR. NEAL.—I think you are doing everything you can. I cannot tell how long it will take him to recover, or if, indeed, he will. I think there is no definite relationship between the cell count and the severity of the illness except that I think most of us have a general impression that cases with a high cell count, that is, the meningeal type of encephalitis, are likely to be rather less severe and less likely to be followed by the chronic stage.

I think there is no relationship between the severity of the acute attack and the probability of the chronic stage developing. Some of the worst chronic types follow initial attacks so light that they were not diagnosed, while some patients under observation for a long time were very severely ill in the acute stage and have failed as yet, at least, to develop the chronic stage.

The meeting adjourned at 4:50 P.M.

Academy News

The following preliminary program has been announced for the Sixth Annual Meeting of the American Academy of Pediatrics to be held Monday and Tuesday, May 11 and 12, at the President Hotel in Kansas City, Mo.

Round Table Discussions

Monday, May 11, 9:30 A.M.

Title	*Leader*
"Asthma"	Francis M. Rackemann, M.D., attending physician, Massachusetts General Hospital, Boston, Mass.
"Childhood Psychiatry"	Franklin G. Ebaugh, M.D., director, Division of Psychiatric Education, The National Committee for Mental Hygiene, New York, N. Y.
"Diagnosis of Appendicitis in Children"	Albert H. Montgomery, M.D., chief surgeon, the Children's Memorial Hospital, Chicago, Ill.

"Intestinal Parasitic Infections"	Ernest Carroll Faust, M.D., professor of parasitology, School of Medicine, Tulane University, New Orleans, La.
"Passive Prophylaxis Against Infection in Childhood"	John A. Toomey, M.D., associate professor of pediatrics, Western Reserve University School of Medicine, Cleveland, Ohio.
"Physical Appraisal of the Child"	Alfred H. Washburn, M.D., director, the Child Research Council, Denver, Colo.
"Prophylaxis and Treatment of Whooping Cough"	E. J. Huenekens, M.D., associate professor of pediatrics, University of Minnesota Medical School, Minneapolis, Minn.
"Recent Advances in Nutrition"	W. McKim Marriott, M.D., professor of pediatrics, Washington University School of Medicine, St. Louis, Mo.
"Roentgenology of the Thorax in Children"	L. R. Sante, M.D., professor of radiology and director of the department of radiology, St. Louis University School of Medicine, St. Louis, Mo.
"Sinusitis—Indications for Treatment"	L. W. Dean, M.D., professor of Otolaryngology and head of the department of otolaryngology, Washington University School of Medicine, St. Louis, Mo.
"Treatment of the Overweight Child"	L. H. Newburgh, M.D., professor of internal medicine, University of Michigan Medical School, Ann Arbor, Mich.

Panel Discussions

May 11, 2:00 P.M.

"Problem of Immunity to Tuberculosis in Childhood"	Chester A. Stewart, M.D., chairman, associate professor of pediatrics, University of Minnesota Medical School.

May 11, 4:00 P.M.

"Cyanosis in the Newborn"	A. Graeme Mitchell, M.D., chairman, professor of pediatrics, University of Cincinnati College of Medicine.

May 11, 8:00 P.M.

Meeting of State Chairmen.

Discussion: "Graduate Education in Pediatrics," Chairman, Borden S. Veeder, M.D.

General Meeting

May 12, 9:30 A.M.

President's Address

Scientific Papers

"The Gastrointestinal Portal of Entry in Poliomyelitis," John A. Toomey, M.D.

"The Clinical Application of the Blood Congulant Extract Obtained From the Human Placenta," R. Cannon Eley, M.D., and Charles F. McKhann, M.D.

Consideration of Reports

(Reports will be presented in mimeograph form to the membership.)

Report of the Executive Board.

Report of the Secretary-Treasurer.

Report of Regional Committees.
Report of Special Committees.
New Business.
Installation of New President.

On May 12, at 2 P.M., the Round Table Discussions will be repeated.

Dr. William B. McClure, of Evanston, Ill., died suddenly of heart disease on February 13.

News and Notes

The following men have been certified by the **American Board of Pediatrics** since the last report.

Dr. Harry Bakwin, New York, N. Y.
Dr. Ruth Morris Bakwin, New York, N. Y.
Dr. Granderson Hearn Bradly, Nashville, Tenn.
Dr. Floyd S. Clarke, Omaha, Neb.
Dr. Wyman C. C. Cole, Detroit, Mich.
Dr. Harry Hampton Donnally, Washington, D. C.
Dr. James Everett Dyson, Des Moines, Iowa
Dr. Fred Leib Glascock, Los Angeles, Calif.
Dr. Alton Goldbloom, Montreal, Canada
Dr. Philip C. Jeans, Iowa City, Iowa
Dr. Edgar J. Huenekens, Minneapolis, Minn.
Dr. Sigurd Herbert Kraft, Chicago, Ill.
Dr. George Marshall Lyon, Huntington, W. Va.
Dr. Katharine Krom Merritt, New York, N. Y.
Dr. Walter Roger Moore, St. Joseph, Mo.
Dr. Lillian Lydia Nye, St. Paul, Minn.
Dr. Martin D. Ott, Davenport, Iowa
Dr. Marshall Carleton Pease, New York, N. Y.
Dr. Bennett Watson Roberts, Durham, N. C.
Dr. Lester Rosenberg, Brooklyn, N. Y.
Dr. Roland P. Seitz, San Francisco, Calif.
Dr. Morton Seldowitz, Brooklyn, N. Y.
Dr. Warren Richards Sisson, Boston, Mass.

The American Board of Pediatrics will conduct the following examinations:

Kansas City, Mo., on May 9, preceding the meeting of the American Medical Association and the American Academy of Pediatrics.

Albany, N. Y., on June 10, preceding the meeting of the American Pediatrics Society.

Baltimore, Md., in November, 1936, at the time of the joint meeting of Region I and Region II of the American Academy of Pediatrics.

Cincinnati, Ohio, in November, 1936, at the time of the Region III meeting of the American Academy of Pediatrics.

San Francisco, Calif., at the time of the Region IV meeting of the American Academy of Pediatrics. Date as yet unannounced.

The next meeting of the **Society for Pediatric Research** will be held at the Chalfonte-Haddon Hall, Atlantic City, N. J., on May 5, 1936. The president is Dr. Charles F. McKhann, and the secretary is Dr. A. A. Weech, New York.

The next meeting of the **Section on Pediatrics of the American Medical Association** will be held in Kansas City, Mo., on May 13, 14, and 15, 1936.

The **American Pediatric Society** will hold its annual meeting at Hotel Sagamore, Bolton Landing, N. Y., on June 11, 12, and 13, 1936. Dr. Fritz B. Talbot is president, and Dr. Hugh McCulloch, secretary. Immediately following the meeting of the Society there will be held exercises for dedication of the Abraham Jacobi Memorial. Further announcement of these exercises will be made later.

The annual meeting of the **South Carolina Pediatric Society** was held at the Francis Marion Hotel, Charleston, S. C., January 28, 1936. Dr. Wilbert C. Davidson, dean of the medical school of Duke University, was the principal speaker. The following officers were elected:

Dr. L. B. Salters, Florence, S. C., president
Dr. Hilla Sheriff, Spartanburg, S. C., vice president
Dr. D. Lesesne Smith, Jr., Spartanburg, S. C., secretary and treasurer

The next meeting of the South Carolina Pediatric Society is to be held in Columbia, S. C., in November, 1936.

A meeting of the **Beardsley Pediatric Club of Connecticut** was held at the State School for Boys at Meriden, February 13, 1936. Dr. Charles I. Soloman, pediatrician-in-charge, presented several cases illustrating the personal and social aspects of juvenile delinquency with special consideration of the behavior and personality changes of children with organic brain disease, such as encephalitis, epilepsy, and cerebral trauma.

Correspondence

London, February, 1936.

Comment has previously been made upon the report of the British Medical Association's Committee on Nutrition. In September, 1935, a booklet entitled "Feeding, Meals, and Catering" was published by the Association. This is in effect a small cookery book based upon the dietary previously recommended for a man, wife, and three children, and is meant essentially for the housewife to whom economic considerations in the feeding of the family are of the first importance. This little booklet is to be welcomed, and has obviously had a very wide appeal, judging by the considerable sale that appears to have followed its publication. It is undoubtedly a great help to those concerned to be supplied with suitable menus in which variety is introduced, even though what at first sight appear to be an unappetizing list of foodstuffs have to be principally employed, for the sake of cheapness.

In November, 1935, meetings were taking place in London of the expert Committee on Nutrition appointed by the Health Committee of the League of Nations, and its report has recently been published. Broadly speaking, their conclusions are of a nature already generally accepted by all concerned in nutritional work and in the scientific feeding and care of children.

Not so long ago considerable anxiety was expressed in some quarters lest children here should be suffering from the results of industrial depression. The Board of Education issued a report which was reassuring, though this was not accepted everywhere. Reports during 1935 continued to be satisfactory, the total figure for malnutrition increasing only by approximately 1 in 1,000; there is, however, striking

dissimilarity in nutritional states from area to area, and from class to class. In London the percentage of subnormal nutrition in 1935 is said to have been lower than ever before.

In this country, school care committees and head teachers select children for free meals, and a scheme also exists for the provision of free milk.

The milk scheme introduced in October, 1934, caused an increase of no less than 256 per cent of those receiving milk for payment and 110 per cent of those receiving it free. It is interesting to note that it is reported that the failure to buy milk at school was caused by poverty in 25 per cent of cases only, that 33 per cent disliked milk, and that in another 24 per cent of cases sufficient nourishment was considered to be obtained at home. There are more than twenty areas in which local education authorities are making provision for free milk during school holidays, and in a few cases also during the week-ends in term time.

In relation to nutrition it is interesting to consider the findings of Dr. A. G. Watkins, who carried out a survey of the physical condition of children between the ages of three and five years in Cardiff and Rhondda schools. These two areas, situated in Wales, differ, the latter coming under the official designation of "distressed area." Watkins's paper, which is worth attention, was published in the *British Medical Journal* in June, 1935. His main conclusions are (1) that there is no single cause of malnutrition; (2) that malnutrition is not common in the areas examined; (3) that endogenous factors have a greater immediate effect on the health than exogenous factors; (4) that an unsatisfactory economic state probably tends to promote the occurrence of ill health, and to prevent adequate convalescent environment and nourishment.

The Board of Education has just issued a circular, giving its views on the development of physical education in the schools and among young people generally. It is of importance and interest to note the attention being paid by public authorities to such methods of training for the purpose of attaining physical fitness in the young members of the community.

The annual report of the Chief Medical Officer to the Board of Education, Dr. Arthur McNalty, has just been published, and will doubtless be referred to by those interested in such aspects of paediatrics, but at any rate one point raised seems worth mentioning here. In discussing dental care, an enquiry in certain districts into children naturally free from dental caries revealed only one safe generalisation: that the regular use of the toothbrush is not essential for freedom from caries. Of 560 children with sound teeth recorded, 104 brushed their teeth irregularly, and 132 never! The dietetic habits of these children gave most bewildering results; all sorts of dietetic errors had been indulged in by those whose teeth were perfect.

The last meeting of the British Paediatric Association was held for the first time in Ireland, at Newcastle, County Down, and proved a tremendous success. A résumé of the proceedings was published during the summer in the *Archives of Disease in Childhood*, and will not therefore be again detailed here. This year's meeting is to be held in England, at Windermere in the Cumberland Lakes District, under the presidency of Dr. Naish of Sheffield; it will take place early in May.

The annual meeting of the British Medical Association is being held in July, and this year is taking place at Oxford. Dr. R. Jewesbury is President-elect of the Children's Section, whose programme includes discussions on the subjects of wasting in infancy and obesity in childhood. In view of the delightful surroundings this year's meeting should be particularly attractive, and no doubt there will be a very large attendance.

K. TALLERMAN.